Chapter 6. Respiratory Health Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and respiratory health from the 1997 OEHHA report and this update are provided below in Table 6.00.

Table 6.00 ETS and Respiratory Disease: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Finding OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
Lung development (children)	8	7 1 meta[a]	Suggestive	Suggestive (strengthened)
Asthma (children) exacerbation	8	14	Conclusive	Conclusive
Respiratory illness (children)	--[b]	9 2 meta	Conclusive	Conclusive
Otitis media ± effusion	22	7	Conclusive	Conclusive
Respiratory symptoms and other effects (children)	6	4	Conclusive	Conclusive
Asthma (children) induction	37	37 1 meta	Conclusive	Conclusive
Asthma (adults[c]) exacerbation	4	7	Suggestive	Conclusive
Sensory irritation and annoyance	18	14	Conclusive	Conclusive
Respiratory symptoms and other effects (adults)	20	5	Suggestive	Suggestive (strengthened)
Asthma (adults[c]) induction	2	11	Suggestive	Conclusive

[a]meta = # meta-analyses – not included in counts of studies. [b]A *de novo* review was not done in 1997 as this topic had been treated recently in reviews of nearly two dozen reports by the NRC, U.S. EPA and Surgeon General. [c]Some studies include adolescents as adults.

6.0. Introduction

The Children's Health Protection Act requires OEHHA to specifically evaluate adverse effects of candidate Toxic Air Contaminants on infants and children. ETS exposure has been shown to induce as well as exacerbate asthma in children, result in decreased lung function in children, and cause respiratory symptoms and illness (including otitis media) in children. There is evidence that postnatal ETS exposure impairs lung development, although the effect appears not to be as great as that from prenatal maternal smoking. ETS exposure also induces and exacerbates asthma in adults, and results in increased respiratory symptoms in adults.

The effects of ETS exposure on non-malignant endpoints of respiratory tract health were examined in the 1997 OEHHA report (Cal EPA, 1997). The conclusions of that report are examined here in light of more recent research on the induction and exacerbation of asthma, otitis media and middle ear effusion in children, lung development and respiratory infections in children, respiratory symptoms and changes in lung function in adults, and sensory irritation and annoyance. The research examined includes both epidemiological and controlled exposure studies with the former representing geographically diverse populations. The more recent studies substantiate the association noted in the previous report between ETS exposure and deleterious respiratory health outcomes.

6.1. Lung Growth and Development (children)

6.1.1. New Epidemiological Findings

The effects of passive smoke exposure on the development of the pulmonary system were investigated in seven studies (Table 6.10). In six studies, spirometric measures showed decrements in lung function with ETS exposure consistent with the meta-analysis by Cook *et al.* (1998) of studies of forced expiratory volume (FEV). Mannino *et al.* (2001) and Bono *et al.* (1998) and Rizzi *et al*. (2004) associated these decrements with high cotinine levels. Elevated neonatal serum cotinine and increased persistent pulmonary hypertension of the newborn were associated with maternal ETS exposure in the study by Bearer *et al.* (1997). As reported in Chapter 4, the study by Elliot *et al.* (1998) found passive smoke exposure to be significantly associated with structural changes in the large airways of SIDS victims. Finally, one study evaluated lung function and symptoms in adults who were exposed as children (Svanes *et al.*, 2004).

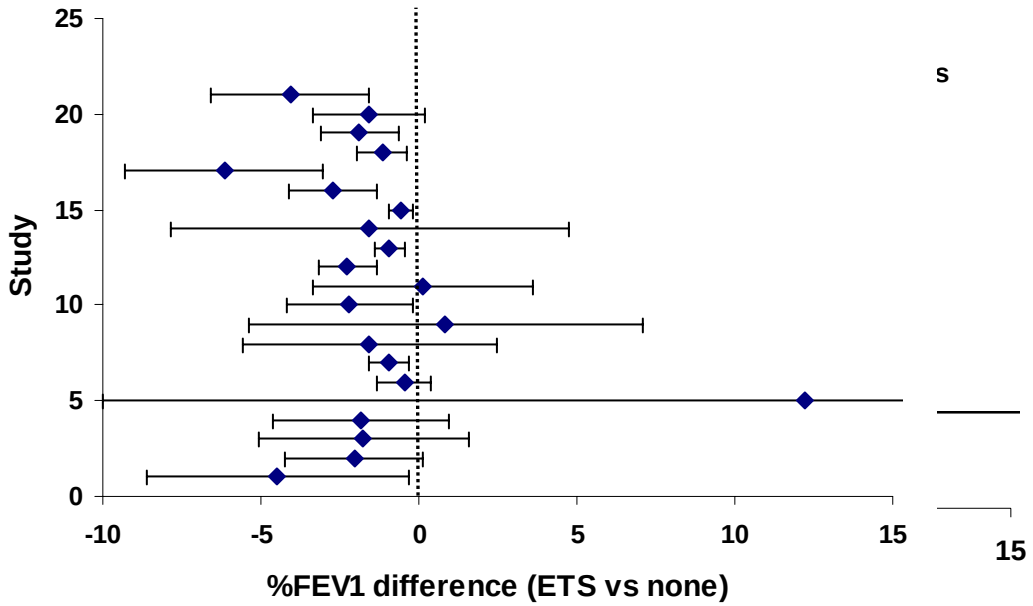
Table 6.10 ETS Effects on Lung Development

Reference Country	Study Description	Exposure To ETS	Outcome and OR (95% CI)	Comments
Meta-analysis				
Cook *et al* 1998 UK	Meta-analysis of 21 studies of lung function in school-age kids	Postnatal	FEV_1 -1.4% (-1.0; -1.9) Mid exp flow -5.0% (-3.3; -6.6) End exp flow -4.3% (-3.1; -5.5)	Small but statistically significant decreases in lung function from maternal ETS. Adj for confounders but can't distinguish pre- and postnatal effects.
Original Studies				
Rizzi *et al.* 2004 Italy	Lung function in adolescent males n=80	Postnatal ETS only. Plus maternal pre-natal smoking	DLCO, Dm, KCO Significantly lower $p< 0.05$ Lower still with prenatal exposure also $p<0.0001$	ETS (as cotinine/creatinine ratio) inversely associated with decrements in lung function. Independent pre- and postnatal effects. Dose response noted.
Svanes *et al*. 2004 Europe	Lung function in adults after ETS in childhood. n=15,901	Parental ETS Maternal smoking	Wheeze OR 1.12 (1.02; 1.23) Asthma symptoms 1.14 (1.02; 1.26) DEV1 decrease $p = 0.012$	Significant risk of pulmonary symptoms in adults exposed in childhood to parental smoking. Effects from both maternal and paternal smoking.
Mannino *et al* 2001 US	Lung function vs serum cotinine in 5400 8-16 yr-olds	Postnatal High vs low cotinine	FEV_1 -1.8% (-3.2; -0.4) MMEF -5.9% (-8.1; -3.4)	Decrements in lung function associated with high vs low cotinine.
Li *et al* 2000 US	Lung function in 5263 7-19 yr olds	Girls/asthma Past ETS only	MMEF -4%	Postnatal ETS exacerbates *in utero* exposure. Prenatal ETS-only effect seen in girls with asthma.
Bek *et al* 1999 Turkey	Cross-sectional study of lung function in 360 9-13 yr olds. Peak and forced expiratory flows and flow after expiration of 50 and 75% capacity.	Postnatal Paternal	FEV_{25-75} −7 % $p = 0.02$ PEF -6% $p = 0.03$ V_{max50} -7% $p = 0.008$ V_{max75} -9% $p =0.009$	Decrements in lung function associated with paternal but not maternal smoking due to unusually low maternal smoking and high paternal-child contact. Limited description of methods and confounder control limit utility of this study.
Bono *et al* 1998 Italy	Studied ETS and rate of change in FEV and FVC in 333 14-16 yr olds	Postnatal	FEV_1 -0.66% $p=0.05$ FVC -0.57% $p=0.082$	ETS as urinary cotinine slowed rate of FEV_1 increase over 1 yr
Bearer *et al* 1997 US	Maternal ETS exposure: persistent pulmonary hypertension of the newborn (PPHN)	Maternal ETS in pregnancy	Blood cotinine PPHN 3.5 ng/ml Ctrl 1.65 ng/ml ($p = 0.022$). OR: 4.68 (1.68; 12.76)	Cotinine levels in newborns associated with ETS exposure and PPHN

CCR cotinine/creatinine ratio; DLCO diffusion capacity for carbon monoxide; Dm diffusion capacity of alveolar membrane; FEF_{25-27} forced expiratory flow at 25-75% of vital capacity; FEV_1 forced expiratory volume in one second; FVC forced vital capacity; KCO carbon monoxide transfer coefficient; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Cook et al., 1998. Part of a series on the health effects of passive smoking, this paper focused on the effect of ETS on spirometry. A meta-analysis was performed on 21 surveys of school-aged children. FEV_1 in children exposed to parental smoking was reduced by 1.4% (95% CI 1.0; 1.9). Mid-expiratory flow rates and end expiratory flow rates were decreased by 5.0% (95% CI 3.3; 6.6%) and 4.3% (95% CI 3.1; 5.5%) when compared to controls. Adjustment for confounding reportedly had little effect on these estimates; however, other than age, gender and height, it is not clear what other factors were evaluated. Individually, these heterogeneous studies show a strong homogeneity of results with nearly all finding decrements in FEV_1 in exposed children (Figure 6.1). This analysis supports the association of maternal smoking with small, statistically significant deficits in spirometric studies in school-aged children. Due to the limitations of available studies, it is not possible to determine the relative effects of prenatal exposure to maternal smoking versus postnatal ETS exposure. In general, this review covers many of the same studies examined in the previous OEHHA document and supports the previous conclusions.

Figure 6.1 Percentage Difference in FEV_1 Between Children of Smokers and Nonsmokers (Data from Cook *et al.*, 1998)



Rizzi et al (2004) evaluated the effects of ETS exposure at home on 80 secondary school students free of chronic respiratory or cardiovascular health problems in Milan (16 ± 1 yrs of age).

Questionnaires were given to students on their own and their parents smoking habits, respiratory health, sociodemographic factors, smokers living in the home, frequency of visiting smoky places, and the overall time exposed to ETS. Cotinine concentration and the cotinine to creatinine ratio of urinary samples were assayed. Lung function measurements and assessments of the diffusion capacity of the lung for carbon monoxide (D_{LCO}) were conducted on each student. The carbon monoxide transfer coefficient (KCO) and alveolar-capillary membrane diffusing capacity (D_M) were calculated. Lung function measurements were compared with predicted values.

Students were classified as smokers (21), passive smokers (29), and nonsmokers (neither parents or students smoked, 30). There were no differences among the groups for height, weight or SES. Cotinine/creatinine increased significantly going from nonsmokers (18.6 ± 9.9 μg/mg) to passive smokers (65.5 ± 23.2 μg/mg) to active smokers (124.7 ± 41 μg/mg) (analysis of variance, $p<0.001$).

Exposure to ETS resulted in deficits in lung function compared to nonsmokers. Compared to nonsmokers, the maximum expiratory flow at 25% of FVC (MEF_{25}) was significantly lower, the residual volume and RV to total lung capacity ratio were significantly greater, and the D_{LCO}, KCO, and D_M were significantly lower in the ETS exposed adolescents. Looking across the three groups, smokers had less lung function than passive smokers who had less lung function than nonsmokers ($p<0.001$).

The authors also looked at those passive smokers whose mothers had stopped smoking during pregnancy and compared their lung function to those whose mothers had not stopped smoking during pregnancy. Their data indicate that *in utero* exposure resulted in larger negative effects than passive smoke exposure postnatally. Specifically, the MEF_{25}, D_{LCO}, KCO, and D_M values for passive smoking adolescents whose mothers smoked during pregnancy were statistically significantly lower than those parameters for passive smokers whose mothers had stopped during pregnancy (all $p<0.05$, unpaired t test).

Finally, comparing the passive smokers with only one household smoker to the passive smokers with more than one household smoker revealed a dose-response trend for MEF_{25}, D_{LCO}, KCO,

and D_M all being significantly lower with multiple smokers than one smoker (all $p<0.01$, unpaired t test).

Thus, this study clearly demonstrates an effect of passive smoke exposure on residual volume and KCO, which suggests alterations in bronchiolar and alveolar structures. Lung function measures indicated mild airway obstruction in the passive smokers (and worse damage in active smokers). The study also found an independent effect of *in utero* exposure from a smoking mother and postnatal exposure to ETS on both spirometric measures and the measures of diffusing capacity.

Svanes et al. (2004) evaluated respiratory health of adults in relation to ETS exposure in childhood. Participating centers in the European Community Respiratory Health Survey randomly selected at least 1500 men and 1500 women from populations of at least 150,000 within defined geographic areas. Information was obtained from self-completed questionnaire as well as more detailed interviews, lung function tests, and blood tests. The paper included analyses of data from 18,922 subjects from 37 centers in 17 countries.

Spirometric data (FEV1 and FVC) were available for 15,901 subjects, and methacholine challenge was performed on 13,206 subjects. Atopy was defined as presence of specific IgE to dust mite, cat, timothy grass, and/or Cladosporium mold (available for 13,972 subjects). Information on parental smoking was collected at interview. Asthma was defined as medication use or asthma attacks in the previous 12 months. Information on respiratory symptoms in the previous 12 months and on chronic bronchitis was also obtained. The relationship between parental smoking in childhood and adult respiratory health was evaluated using logistic regression models with adjustments for age, gender, body mass index, current smoking, current ETS exposure, occupation, and others.

Maternal smoking was statistically significantly associated with an increased risk of wheeze (OR1.12; 95%CI 1.02-1.23), presence of more than 3 asthma symptoms in the previous 12 months (OR 1.14; 95%CI 1.02-1.26), chronic bronchitis (OR 1.19; 95%CI 1.05-1.35), decreases in FEV1 ($p=0.012$), and in the FEV/FVC ratio ($p<0.001$), when men and women were combined. Maternal smoking during pregnancy was also associated with statistically significant OR for wheeze (OR 1.24; 95%CI 1.09-1.42), more than 3 asthma symptoms (OR1.28; 95%CI 1.11-1.48;

and chronic bronchitis (O$1.32; 95%CI 1.11-1.57) In addition, there was a statistically significant decrease in the beta coefficient for FEV1/FVC ratio (-0.99; 95%CI –1.3 to -0.5; p<0.001). It should be noted that 40% of the subjects reported not knowing whether their mother had smoked during pregnancy, so this analysis includes only about 60% of the respondents. When only nonsmokers were evaluated (about 3000 men and 3500 women), there were similar elevations but most did not attain statistical significance.

When paternal smoking was evaluated, an association was noted between adult respiratory symptoms and lung function in men but not in women. The OR for wheeze in adult men associated with paternal smoking in childhood was 1.13 (95%CI 1.00-1.28; p<0.058), while that for more than 3 asthma symptoms was 1.20 (95%CI 1.03-1.39; p<0.022), and for chronic bronchitis was 1.22 (95%CI 1.02-1.45); p<0.031). The authors note that there is a convincing effect of postnatal exposure to ETS on lung health in adult men.

Maternal smoking was associated with both symptoms and lung function decrements in women, but less so in men. In women the odds ratios were 1.14 (95%CI 1.01-1.31; p<0.032) for wheeze, 1.16 (95%CI 1.01-1.33; p<0.040) for more than 3 asthma symptoms, and 1.22 (95%CI 1.01-1.46; p<0.035) for chronic bronchitis. Statistically significant decrements in FEV1 and in the ratio of FEV1 to FVC were noted.

This study also evaluated whether there was evidence of a dose-response by looking at the differences between results when only one parent smoked or when both parents smoked. For men and women combined, there was a significant trend upwards for both lung function decrement and symptoms when both parents smoked. This was also the case when men were considered separately, but only one trend test was positive when women were considered separately.

This study did not separate the effects of maternal postnatal exposure with intrauterine exposure to smoke constituents from maternal smoking. Paternal smoking appeared to have no effect on women’s adult lung health, but did affect men’s adult lung health. The authors’ speculate that there may be gender differences in the window of susceptibility for effects of tobacco smoke constituents on the lung, with females being more susceptible to prenatal damage and males

more susceptible to postnatal damage. However, additional study would be needed to elucidate evaluate that hypothesis.

Mannino et al., 2001. This study from the Centers for Disease Control utilized data on 5,400 US children collected from the NHANES III, a nationally representative cross-sectional survey. Pulmonary function studies were performed in children 8–16 years of age. Logistic and linear regressions of serum cotinine levels were stratified into tertiles and pulmonary function tests adjusted for age, height, ethnicity, SES, parental history of allergy or asthma, family size, maternal prenatal smoking and cotinine levels. Decrements in lung function were noted with high cotinine compared with low cotinine levels, with a mean change of -1.8% (95% CI -3.2; -0.4%) in FEV_1, and a mean change of -5.9% (95% CI, -8.2; -3.4%) in MMEF. Lower levels of lung function were also associated with a history of prenatal exposure to maternal smoking. A limitation of this study is the relatively short half-life of cotinine (3-4 days) making this an accurate evaluation of recent exposure but not long-term exposure. It is assumed that lifetime exposure is likely to be more accurately expressed by this in the youngest age groups. The study is strengthened by the large sample size, the representative nature of the population, use of biomarkers, adjusting for covariates and evaluation of potential confounders.

Li et al., 2000. Lung function was measured spirometrically on 5,263 children, ages 7-19 yrs, who participated in the University of Southern California Children's Health Study. Health, demographic and ETS exposure data were collected at enrollment. Forced vital capacity (FVC), forced expiratory volume (FEV) and maximum mid-expiratory flow (MMEF) were measured. ETS exposure was associated with deficits in lung flows and increases in lung volumes. These effects were also seen to be influenced by *in utero* exposure, children's gender and asthma status. *In utero* exposure to maternal smoking generally had a larger effect on lung function. A significant effect of exclusively postnatal ETS exposure was only observed in girls with asthma as a 4% deficit in MMEF. Current ETS exposure was found in this study to be detrimental to lung function although the measured effects were small and often not statistically significant after adjustment for *in utero* exposure. However these data were a cross-sectional sampling of a longitudinal study and there was no adjustment made for changes in parental smoking behavior nor for ETS exposure outside the home. Either situation would be expected to alter estimates of ETS effects, likely diluting the sensitivity of the study.

Bek et al., 1999. These investigators conducted a cross-sectional study in Turkey to evaluate the effect of ETS on lung function studies in 360 children 9-13 years. Information was obtained via a questionnaire and spirometry. Paternal smoking was associated with and 7% (p=0.02) reductions in FEV_{25-75} , ,a 6% (p=0.03) reduction in peak expiratory flow, and 7% (p=0.008) and 9% (p=0.009) reductions in V_{max50} and $V_{max\ 75}$, respectively (flow rates after 50 or 75% of the vital capacity is expired). The description of methods is limited and it appears that confounding variables were not adequately considered limiting the usefulness of this study.

Bono et al., 1998. The effects of ETS on lung growth were determined by the rate of increase in measurements of FEV_1 and FVC taken in two consecutive years and related to urinary cotinine levels in this longitudinal study of 333 school children, ages 14-16. After controlling for changes in age, height, weight and smoke exposure between measurements, ETS exposure, as measured by urinary cotinine levels, was associated with a reduction in rate of increase of 0.66% for FEV_1 (p=0.05), and of 0.57% in FVC (p=0.082). Due to the narrowness of the developmental window during which these measurements were made, it is not known whether these small decrements in lung function growth are permanent and/or whether they become more pronounced with longer-term exposure. Nevertheless, the data indicate that ETS has at least a transient deleterious affect on lung function development.

Bearer et al., 1997. Persistent pulmonary hypertension of the newborn (PPHN) is a clinical disorder associated with remodeling of the pulmonary vasculature and elevated risk of perinatal death. It is characterized by abnormal vascular structure, growth and reactivity. The association between maternal and fetal nicotine exposure (cotinine levels) and PPHN was the topic of this study. Cotinine was assayed in cord blood or the earliest sample of newborn blood. PPHN was indicated by the lability of oxygenation and/or disparity of pre- and postductal oxygen saturation as assessed by pulse oximetry and confirmed by two-dimensional echocardiography. Thirty-one PPHN case infants were compared with 39 controls. Mothers were matched for ethnicity and there were no significant differences between groups for age, education, parity or gravidity. In the PPHN group, Apgar scores at 1 and 5 minutes were significantly lower ($p<0.0001$) and detectable cotinine was higher (5.2 ng/ml) than in the comparison group (2.0 ng/ml). Among those reporting passive smoke exposure only, continine was detected in 50% of the PPHN infants versus 18% of the comparison group, with a significantly higher median value for the

PPHN group (3.5 ng/ml vs 1.65 ng/ml; p=0.022). Logistic regression analysis was performed to correct for baseline differences in the groups and for potential selection bias, and resulted in an unadjusted OR of 4.68 (95% CI 1.679; 12.755; p = 0.0086) for the association of passive smoke exposure and PPHN. The OR for PPHN reportedly increased to 6.10 after adjustment for ethnicity but no confidence interval was provided.

6.1.2. Studies on Lung Development in Animals

Recent studies of lung development in animals have concentrated on the effects of maternal ETS exposure during pregnancy on subsequent development in the fetus and neonate. In a study by Nelson *et al.* (1999), histological changes were observed in the lungs of neonatal rats born to mothers exposed to sidestream smoke during pregnancy. Increasing changes in the mesenchyme and incidence of apoptosis in neonatal lungs were seen with increasing exposure of the dam to sidestream smoke (1-4 cigarettes/day for 1 week), especially when the exposure occurred during the third versus first or second week of gestation.

ETS has been implicated in the development of reactive airway disease. As described in section 6.5.1.4, a study by Rumold *et al.* (2001) used a murine model to test whether exposure to side stream smoke (SS; a surrogate for ETS) can induce allergic sensitization to inhaled ovalbumin (OVA). In this study, both total serum and OVA-specific IgE levels were significantly elevated in mice exposed to OVA/SS compared to OVA alone ($p<0.01$). Similarly IgG1 levels were significantly elevated in this group ($p<0.01$). The production of specific allergic antibodies to inhaled allergens is characteristic of the sensitization phase of reactive airway disease. These experiments indicate that ETS has the capacity to alter lung homeostasis and augment allergic sensitization to otherwise innocuous allergens.

In addition to allergic sensitization, ETS exposure may also render lungs more susceptible to subsequent injury by ozone. Yu *et al.* (2002) collected bronchoalveolar lavage (BAL) fluid and lungs from adult B6C3F1 mice exposed to aged and dilute sidestream smoke (ADSS), filtered air, ozone or ADSS followed by ozone. Exposure to ADSS (112 ppm CO, 29.5 mg/m^3 total suspended particulate) was for 6 hrs/day on three consecutive days. Cell proliferation in the lungs, as measured by bromodeoxyuridine (BrdU) incorporation, was used as an indicator of cell injury and death. BrdU incorporation was signficantly elevated by ozone exposure compared to

filtered air or ADSS ($p < 0.05$), and was further significantly elevated after exposure to the combination of ADSS and ozone compared to ozone alone ($p < 0.05$). Similarly, in the BAL fluid, neutrophils were increased by ozone compared to air or ADSS ($p < 0.05$), with neutrophils, macrophages and protein significantly more abundant after ADSS and ozone combined than after ozone alone ($p < 0.05$). This indicated that prior smoke exposure exacerbated the cellular damage caused by ozone exposure.

6.1.3. Summary of ETS Effects on Lung Growth and Development

Childhood exposure to ETS was found to be associated with small decrements in various spirometric measures of lung function in pre-adolescents and adolescents in the range of 0.5-7%. One study demonstrated decreased diffusing capacity in passive smokers (Rizzi *et al.*, 2004). In addition, in at least one study, childhood ETS exposure was associated with respiratory symptoms and lung function in adults (Svanes *et al.,* 2004). From most of these studies it is not possible to determine the contribution of prenatal exposure to the observed effects. However, there are a few exceptions. Li *et al.* (2000) observed an independent effect of postnatal ETS exposure but found that prenatal passive smoke exposure had a more pronounced effect on lung function than did postnatal ETS. In addition, Li *et al.* observed that *in utero* exposure combined with asthma resulted in significantly larger deficits than in children without asthma. Rizzi *et al.* (2004) found that *in utero* exposure resulted in larger lung function decrements than did postnatal exposure alone. Svanes *et al*. (2004) found that paternal smoking, but not maternal smoking was more strongly associated with lung function decrements in men but not in women. Thus postnatal ETS exposure appears to have possibly influenced men's adult lung health in this study, separate from *in utero* exposure. In three studies (Mannino *et al.*, 2001; Bono *et al.*, 1998; Bearer *et al.*, 1997), ETS exposure was documented by measurements of cotinine, an indicator of recent nicotine exposure, and an association was found between the adverse effects and elevated cotinine; thus, these studies implicate postnatal ETS exposure as causing decreased lung function growth. It is evident that childhood ETS exposure is at least transiently detrimental to lung development, and if the effects seen in Svanes *et al*. (2004) are repeated in other studies, the effects may indeed be permanent.

Consistent with the adverse effects reported for ETS exposure are studies of the effects of ambient air pollution. In an eight-year prospective study of 1,759 children recruited at 10 years

of age in southern California, deficits in the growth of FEV_1 were significantly associated with exposures to components of ambient air pollution, specifically NO_2 ($p = 0.005$), acid vapor ($p = 0.004$), $PM_{2.5}$ ($p = 0.04$) and elemental carbon ($p = 0.007$) (Gauderman et al., 2004). Thus the plausibility of an adverse effect of ETS exposure on lung development is borne out by studies of the effects of air pollution on the same endpoints. In addition, these lung function changes can be considered permanent as the growth in lung function is essentially complete in an 18 year old.

6.2. Acute Health Effects in Children

6.2.1. Asthma Exacerbation

6.2.1.1. Previous Findings on Asthma in Children

A previous review by U.S. EPA (1992) concluded that: "There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease." The 1997 Cal/EPA report, which reviewed additional studies, affirmed the causal connection between ETS exposure and childhood asthma exacerbation.

6.2.1.2. New Epidemiological Findings in Children

Fourteen more recent cross-sectional and cohort studies are described below and summarized in Table 6.20. Recent publications continue to confirm the adverse impact of ETS exposure on childhood asthma status.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Gilliland *et al.* 2003 US	Absenteeism among fourth-graders related to respiratory illness. n = 1,932	Parental smoking vs child ± asthma None + asthma 1 + no asthma 1 + asthma ≥ 2 + no asthma ≥ 2 + asthma	Absenteeism due to respiratory illness 1.45 (1.15; 1.83) 1.05 (0.79; 1.39) 2.35 (1.49; 3.71) 1.44 (1.04; 2.00) 4.45 (2.80; 7.07)	ETS increases absences due to respiratory illness as does asthma. ETS from ≥ 2 smokers exacerbates absentee risk 3-fold in asthmatic children.
Mannino *et al* 2002 NHANES III US	Population-based study cross-sectional: serum cotinine and asthma severity 4-6 yrs n = 523	Serum cotinine Highest vs lowest tertile	Moderate to severe asthma 2.7 (1.1; 6.8) FEV1 -8.1% (-14.7; -3.5%) FVC -5.6% (-10.6; -0.6%) FEV1/FVC -3.0% (-6.5; 0.5%)	Highest cotinine levels associated with moderate to severe asthma; also with severe asthma but CI included no effect.
Crombie *et al* 2001 UK	Retrospective cohort study: salivary cotinine vs health service contacts among asthmatic kids. 2-12 yrs. n = 438	Salivary cotinine. ≤ 2 ng/ml 2.1– 4.5 “ > 4.5 “	Health service contacts 1.0 (ref) (IRR[1]) 0.95 (0.82; 1.11) 1.15 (0.98; 1.34)	Measured ETS exposure for period following 12 months of tracked health service contacts.
Ehrlich *et al* 2001 S Africa	Cross-sectional study: urinary cotinine in 2nd grade asthmatics and bronchial hyperresponsiveness (BHR) n = 249	Urinary cotinine 33.8 ng/mg 34-74.2 “ 74.3- 137.7 “ > 137.7 “	BHR PR[2] (referent) 0.86 (0.61; 1.20) 0.94 (0.68; 1.30) 0.81 (0.57; 1.15)	BHR not associated w/ETS. But parents of symptomatic children may decrease smoking.

[1] IRR incident rate ratio [2] PR prevalence ratio BHR bronchial hyperresponsiveness; FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Venners *et al* 2001 China	Cross-sectional study: paternal smoking and pulmonary function in asthmatic kids 8-15 yrs, n = 529	Paternal < 30 cig/day ≥ 30 " < 30 cig/day ≥ 30 "	FEV_1 Girls -18 ml (p=0.75) -24 ml (p=0.73) FEV_1 Boys -38 ml (p=0.40) -72 (p=0.24)	Compared to nonsmoking fathers, statistically nonsignificant decrease in FEV_1 with increased paternal smoking. Dose-dependent trend suggested.
Melen *et al* 2001 Sweden	Cohort study: 2 yr follow-up of severe asthma attacks 1-4 yrs. n = 181	Parent reported Severe asthma ETS synergism w/dust mite allergen	Severe asthma 3.0 (0.74; 12.2) 18 (3; 101)	ETS associated with risk of severe asthma. ETS synergistic w/ dust mite allergen OR 18 (3; 101).
Willers *et al* 2000 Sweden	Cross-sectional study: asthma symptoms vs cotinine 8-11 yrs. n = 87	Plasma cotinine Asthma+wheeze " " +dyspnea previous asthma Urinary cotinine Asthma+wheeze " " +dyspnea previous asthma	median cotinine 0.50 µg/l plasma 0.80 µg/l plasma 0.60 µg/l plasma 0.60 µg/g creatinine 1.60 µg/g " 0.70 µg/g "	Current asthma with wheeze and dyspnea associated with highest cotinine in urine and plasma but significance unknown as study lacked statistical comparisons.
Schwartz *et al.* 2000 Finland	Cohort study: followed ETS and PEF in asthmatic kids for 3 mo 7-12 yrs n = 74	Parent diary Any vs none Daily PEF l/min Evening PEF Mean decrement PEF Bronchodilator use Cough Phlegm production.	PEF decrement Any vs no ETS -42 (-10 to –74) -41 (-8 to –74) ETS previous day 9.2 (-2.9 to 21) 10.3 (1.3 to 84) 12.4 (2.4 to 63) 7.8 (1.4 to 42)	ETS associated with decreased peak expiratory flow (PEF) both morning and evening. Also exposure-response trend for days of ETS and PEF (p=0.01)

FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Li *et al* 2000 US	Cross-sectional study: pulmonary function among asthmatic kids 7-19 yrs n = 749	Parent reported Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal	FEV_1 (ml) Boys -2.7 (-8.1; 3.0) -0.4 (-5.5; 4.9) -6.8 (-13.8; 0.7) -7.2 (-11.4; -2.8) FEV_1/FVC Boys -0.6 (-3.8; 2.8) -1.7 (-4.6; 1.4) -5.0 (-9.2; -0.6) -2.8 (-5.4; -0.1) MMEF Boys -2.8 (-14.2; 10.0) -2.9 (-13.3; 8.6) -14.0 (-27.3; 1.7) -11.0 (-19.5; -1.6) FEV_1 (ml) Girls 2.7 (-2.1; 7.8) 3.3 (-1.5; 8.3) 1.3 (-5.7; 8.9) 0.2 (-3.4; 4.0) FEV_1/FVC Girls 2.4 (-0.8; 5.7) 0.9 (-2.2; 4.1) -6.8 (-11.2; -2.3) -2.6 (-4.9; -0.1) MMEF Girls 10.3 (-0.9; 22.7) 10.2 (-0.9; 22.5) -17.1 (-30; -2.6) -3.5 (-11.3; 5.0)	*In utero* exposure in boys strongly associated with decreased pulmonary function (FEV_1) especially if combined with postnatal ETS compared to no parental ETS. Postnatal effect not evident for girls or other function measures.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Oddoze *et al* 1999 France	Cross-sectional study: urinary cotinine vs BHR in asthmatic kids hospitalized w/wheeze. 4-14 yrs. n = 90	Urinary cotinine	Cotinine inversely associated with amount carbachol that doubled airway resistance	Same group as Dubus study with similar results but no effect estimates. p = 0.03
Dubus *et al* 1998 France	Cross-sectional study: urinary cotinine in asthmatic kids and BHR 5-13 yrs. n = 46	Urinary cotinine undetectable elevated	Carbachol to double airway resistance 161 µg 108 µg	ETS exposure increased BHR, as less carbachol was needed to double airway resistance. p = 0.04
Abulhosn *et al* 1997 US	Cohort study: follow-up for 4 wks after hospitalization for asthma 2-13 yrs n = 22	Parent reported Symptomatic Days Nights ß-agonist use/wk	ETS vs none (days) 3.3 vs 1.4 ($p<0.05$) 2.3 vs 1.4 ($p>0.05$) 3 vs –12 ($p<0.001$)	During 4 wk recovery, ETS-exposed had more symptomatic days and no decrease in ß-agonist use vs decrease of 12 x/wk w/no ETS.
Meijer *et al* 1996 US	Cohort study: followed PEF amplitude and ETS after withdrawal of inhaled corticosteroids. 9.3 yrs n = 55	Parent report	Circadian PEF amplitude increase ß = 11.2 (p=0.001)	ETS increased variation in PEF (amplitude) suggesting effects on airway diameter.
Macarthur *et al.*, 1996 Canada	Cohort study: followed ETS vs rehospitalization of asthmatic kids. 1-13 yrs n = 68	Parental smoking assessed from hospital records	Rehospitalization OR 1.4 (0.9; 2.4)	ETS increased risk of re-hospitalization but accuracy of exposure assessment questionable.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Gilliland et al., (2003). evaluated the relationship between ETS exposure, asthma status and illness-related absenteeism in the Southern California Children's Health Study, a cohort of 1,932 fourth-grade children in 12 California. Data on sociodemographics, indoor exposures and medical histories were obtained from parents or guardians via questionnaires at study entry. Attendance data were collected from the schools, and parents were contacted by telephone to determine the reason for the absence. Illness-related absences were categorized into respiratory or gastrointestinal. To estimate the risk of absenteeism associated with ETS exposure, incident absence rates were stratified and adjusted for sociodemographic variables including community, ethnicity, age, gender, parental education, health insurance, family income, BMI, and number of hours of outdoor activity.

Any ETS exposure was found to significantly increase the incidence of missed school days, including non-illness-related (RR 1.29, 95% CI 1.02; 1.63), illness-related (RR 1.33, 95% CI 1.13; 1.57), and respiratory-illness-related (RR 1.27, 95% CI 1.04; 1.56) absences. Among illness-related and especially respiratory-illness-related absences, there was evidence of dose-response relationships associated with increasing numbers of smokers in the household. Children with asthma or wheeze were particularly sensitive to ETS. The risk of absenteeism for respiratory-related illness among asthmatic children not exposed to ETS was 1.45 (95% CI 1.15; 1.83) compared to 4.45 (95% CI 2.80; 7.07) with exposure to two or more smokers (see Table 6.21). A similar trend was observed among children with wheeze. Exposure to ETS was also associated with an enhanced risk of absence due to gastrointestinal illness (RR 1.43; 95% CI 1.12; 1.82) that increased as the number of household smokers increased.

These data indicate that ETS exposure has a significant deleterious effect on children's health as measured by school absenteeism. Since even non-illness-related absences were higher among ETS-exposed children, it may be expected that ETS exposure may negatively affect scholastic performance and academic achievement in addition to its adverse health effects.

Table 6.21 ETS exposure and School Absenteeism

	#Children	Non-illness related	Illness-related	Respiratory-illness-related
ETS/asthma		RR (95% CI)	RR (95% CI)	RR (95% CI)
No/No	1,264	ref	ref	ref
No/Yes	217	0.82 (0.58; 1.16)	1.30 (1.06; 1.59)	1.48 (1.17; 1.81)
Yes/No	303	1.23 (0.96; 1.59)	1.25 (1.04; 1.50)	1.14 (0.91; 1.44)
Yes/Yes	48	1.21 (0.69;2.14)	2.19 (1.59; 3.01)	2.55 (1.78; 3.65)
#Smokers/asthma				
0/No	1,294	ref	ref	ref
0/Yes	226	0.91 (0.66; 1.26)	1.27 (1.04; 1.55)	1.45 (1.15; 1.83)
1/No	209	1.40 (1.05; 1.87)	1.18 (0.95; 1.47)	1.05 (0.79; 1.39)
1/Yes	30	1.26 (0.63; 2.53)	2.02 (1.35; 3.00)	2.35 (1.49; 3.71)
≥ 2/No	98	1.31 (0.90; 1.92)	1.46 (1.12; 1.89)	1.44 (1.04; 2.00)
≥ 2/Yes	17	1.51 (0.64; 3.59)	3.29 (2.16; 5.03)	4.45 (2.80; 7.07)
ETS/Wheeze				
No/No	968	ref	ref	ref
No/Yes	467	1.28 (1.01; 1.61)	1.26 (1.08; 1.47)	1.45 (1.20; 1.75)
Yes/No	218	1.27 (0.94; 1.73)	1.14 (0.92; 1.42)	0.93 (0.69; 1.25)
Yes/Yes	124	1.59 (1.11; 2.26)	1.90 (1.50; 2.39)	2.29 (1.75; 3.00)
#Smokers/Wheeze				
0/No	992	ref	ref	ref
0/Yes	480	1.32 (1.05; 1.66)	1.25 (1.07; 1.47)	1.43 (1.18; 1.73)
1/No	159	1.46 (1.04; 2.05)	1.08 (0.93; 1.41)	0.89 (0.62; 1.27)
1/Yes	75	1.71 (1.11; 2.62)	1.81 (1.36; 2.41)	2.13 (1.53; 2.97)
≥ 2/No	61	1.49 (0.93; 2.39)	1.43 (1.03; 2.00)	1.20 (0.76; 1.88)
≥ 2/Yes	51	1.49 (0.88; 2.50)	2.21 (1.62; 3.02)	2.97 (2.09; 4.23)

Mannino et al., 2002. Using the population-based NHANES III data, Mannino and colleagues examined the impact of ETS exposure, as measured by serum cotinine, on asthma severity, which was classified based on frequency of respiratory symptoms and illnesses. Compared to the lowest serum cotinine tertile, the highest cotinine tertile was associated with a greater risk of moderate or severe asthma (OR 2.7; 95% CI 1.1; 6.8). The risk of severe asthma was also elevated, but the confidence interval was wide and included no difference (OR 1.9; 95% CI 0.6; 5.7). The highest cotinine tertile was also related to decreased pulmonary function, including a lower mean FEV_1 (-8.1%; 95% CI -14.7%; -3.5%), FVC (-5.6%; 95% CI -10.6%; -0.6%), and FEV_1/FVC ratio (-3.0%; 95% CI –6.5%; 0.5%).

Crombie et al. (2001) evaluated the relationship between current salivary cotinine and health service contacts for asthma during the previous year. These investigators recruited 438 children aged 2-12 with asthma and one or more smoking parents from general practices in the

U.K.Health contacts were determined by review of medical records and computerized pharmacy records. Compared to the lowest cotinine group, the highest cotinine group was associated with an increased risk of health care utilization for asthma expressed as the incident rate ratio (IRR 1.19; 95% CI 1.05; 1.37). After controlling for asthma severity and sociodemographic covariates, the risk estimate was slightly lower (IRR 1.15; 95% CI 0.98; 1.34). A major limitation of this study is the nature of the exposure-outcome relationship. Because ETS exposure was ascertained for a period following the health care utilization, the causal pathway may not be clearly delineated. For example, the parent of a child with frequent asthma-related utilization may reduce their smoking, which would attenuate the risk estimate.

Ehrlich et al., 2001. In a population-based cross-sectional study from South Africa, researchers recruited a sample of 249 second-grade students with asthma to undergo bronchoprovocation testing with histamine. There was no statistical relationship between urinary cotinine-creatinine ratio and the risk of bronchial hyperresponsiveness. Similarly, there was no association between self-reported current maternal or paternal smoking and the prevalence ratio (PR) for bronchial hyperresponsiveness (PR 0.8; 95% CI 0.5; 1.1 and PR 1.0; 95% CI 0.8; 1.3). There was also no relation between cotinine-creatinine ratio and an asthma symptom score (p=0.40). Current maternal smoking was associated with lower mean FEV1 (mean decrement –232 ml; 95% CI –461; -2). This relationship was not observed for current paternal smoking (mean FEV1 increment 112 ml; 95% CI –78; 302). Overall, the study results support a negative impact of ETS exposure on pulmonary function, but not on bronchial hyperresponsiveness or asthma severity. As the authors point out, parents with symptomatic children may be more likely to quit smoking or not smoke around the child, which would attenuate the observed risk.

Venners et al., 2001. In a study from rural China, researchers using a cross-sectional design examined impact of paternal smoking on pulmonary function among 529 children with asthma. Because maternal smoking was rare, this study was able to independently evaluate the impact of paternal smoking. Exposure to paternal smoking was associated with decreased FEV_1 in both boys and girls, although the results were not statistically significant (Table 6.20). Inspection of the results suggests an exposure-response relationship. These results, based on a rural Chinese population, should be generalized to the California population with caution.

Melen et al. (2001) evaluated a cohort of 181 Swedish children with asthma two years after they were enrolled in an earlier case-control study. These children were initially recruited from pediatric allergy clinics in Stockholm for evaluation of asthma. Many had been hospitalized or seen in an emergency department for asthma. At follow-up, asthma severity was classified using structured interview data from parents, based on current asthma symptoms and level of inhaled corticosteroid use. Severe asthma was defined as daily regular corticosteroid use and activity restriction for more than 6 days/month (12 children met this definition at follow-up). Parental smoking was associated with a greater risk of severe asthma at 2-year follow-up (OR 3.0; 95% CI 0.74; 12.2). Because the proportion of children with severe asthma was low, the confidence intervals are wide. In addition, the authors observed a synergistic interaction between high levels of dust mite allergen in the home and ETS exposure at baseline (OR for both factors 18.0; 95% CI 3.0; 101).

Willers et al. (2000) recruited 85 of 137 children with asthmatic symptoms who were identified by a population-based survey. They evaluated the relationship between ETS exposure (plasma and urine cotinine levels) and asthma symptoms. Compared to children who indicated previous (but not current) asthma symptoms, subjects with current wheeze had similar plasma cotinine levels (median 0.50 µg/l vs. 0.60 µg/l). The results for urine cotinine-creatinine ratios were also similar (0.60 µg/g creatinine vs. 0.70 µg/g). Children with current wheeze and dyspnea had higher plasma and urinary cotinine levels (median 0.80 µg/l and 1.6 µg/g creatinine, respectively). In particular, children with current wheeze and dyspnea appear to have higher urine cotinine-creatinine ratios than children with wheeze alone. Although no statistical comparisons are presented, these results were deemed "not statistically significant" by the authors. The lack of detailed statistical comparisons among the groups limits interpretation of this study.

Schwartz et al., 2000. Researchers recruited 74 asthmatic children, using a survey sent to primary school children in 8 schools in Kuopio, Finland. Participants were instructed to record daily respiratory symptoms, medication use, and ETS exposure in the home every day for a 3-month period. In addition, children measured their peak expiratory flow each morning and evening. As assessed by the diaries, any ETS exposure during the 3-month period was associated with a lower peak expiratory flow in the morning (mean decrement 42 L/min; 95% CI

10; 74) and evening (41 L/min; 95% CI 8; 74). This mixed effects regression analysis controlled for socioeconomic factors, height, asthma medications, and repeated measurements among subjects. There was also evidence of an exposure-response relationship between number of ETS exposure days and peak expiratory flow (p for trend = 0.01). When 1-day lagged ETS values were examined, the relationship between ETS and decreased peak expiratory flow was less strong (mean decrement 9.2 L/min; 95% CI 2.9; 21). 1-day lagged ETS exposure was strongly related to a greater risk of subsequent bronchodilator use (OR 10.3; 95% CI 1.3; 84), cough (OR 12.4; 95% CI 2.4; 63), and phlegm production (OR 7.8; 95% CI 1.4; 42). This study clearly supports an association between ETS exposure and exacerbation of asthma.

Li et al., 2000. A cross-sectional analysis, using children recruited for the University of Southern California Children's Health Study, examined the relationship between ETS exposure (past and current) and pulmonary function among 749 children aged 7-19 years with current asthma. Compared to boys without any parent-reported ETS exposure, a history of *in utero* tobacco exposure (i.e., maternal smoking) was most strongly associated with decreased FEV_1, FEV_1/FVC ratio, and maximal mid-expiratory flow (MMEF) (Table 6.20). Both past and current ETS exposures were related to lower pulmonary function values, but the confidence intervals were wide and included no effect. Boys exposed to two or more current smokers had lower FEV_1 (-2.9 ml; 95% CI –9.0; 3.7), FEV_1/FVC ratio (-3.6 ml; 95% CI –7.2; 0.1), and MMEF (-5.2 ml; 95% CI –18; 9.5). The combination of *in utero* tobacco exposure and any postnatal ETS exposure was associated with statistically significant decreases in FEV_1 (-7.2 ml; 95% CI –11.4; -2.8), FEV_1/FVC (-2.8 ml; 95% CI -5.4; -0.1), and MMEF (-11.0 ml; 95% CI –19.5; –1.6). In girls, *in utero* tobacco exposure alone was associated with decreased FEV_1/FVC and MMEF, but not FEV_1. The combination of *in utero* tobacco exposure and subsequent ETS exposure was associated with a statistically significant decrease in FEV_1/FVC (-2.6; 95% CI -4.9; -0.1) and an apparent, but not statistically significant, decrease in MMEF (-3.5 ml; 95% CI -11.3; 5.0). Exposure to two or more smokers was associated with a decrease in FEV_1/FVC (-2.7 ml; 95% CI -6.0; 0.6) and MMEF (-4.2 ml; 95% CI -14; 7.2), but not to FEV_1 (2.7 ml; 95% CI -2.3; 7.8). Taken together, these data support the subacute or chronic negative effects of ETS exposure on pulmonary function among children with asthma.

Oddoze et al., 1999. Another study from the same French investigators examined pulmonary function among 90 children recruited from a pediatric asthma clinic or who were recently hospitalized for wheezing. Although no effect estimates were presented, the authors noted a strong positive association between urinary cotinine and the degree of bronchial hyperresponsiveness as measured by the response to carbachol (p=0.03). They reported no relationship between urinary cotinine and FEV_1 (no specific results presented).

Dubus et al. (1998) recruited 46 children (ages 5-13 years) with asthma who were referred to a pulmonary function laboratory. Based on urinary cotinine levels, they divided children into ETS-exposed (elevated urine cotinine) vs. unexposed (no detectable cotinine). The ETS-exposed children had greater bronchial hyperresponsiveness, as indicated by a lower dose of inhaled carbachol that doubled specific airway resistance (mean 108 μg vs. 161 μg). In contrast to the study by Ehrlich and colleagues (Ehrlich *et al.*, 2001), these results are consistent with an adverse effect of ETS exposure on bronchial hyperresponsiveness. While there was no assessment of a child's smoking history, it seems unlikely that this would have influenced the association observed in this study, since not many children younger than 10 or 12 smoke.

Abulhosn et al. (1997) followed a cohort of 22 children for 4 weeks following hospitalization for asthma. Based on parent responses, children were classified as living in homes with any smokers (exposed) vs. none (unexposed). After hospital discharge, ETS-exposed children had more symptomatic days from asthma than unexposed children (mean ± SEM 3.3 ± 3.7 symptomatic days vs. 1.4 ± 2.1 days, $p < 0.05$). Children with ETS exposure also had more symptomatic nights (mean 2.3 ± 3.4 vs. 1.4 ± 1.9), although the p value was greater ($p > 0.05$). After hospitalization, ETS-exposed children had no significant change in weekly bronchodilator use (mean increase 3.0 dose/week), whereas unexposed children had a reduction in weekly use (mean reduction 12 doses/week, $p < 0.001$). This study indicates that among children with a severe asthma exacerbation that requires hospitalization, ETS exposure is associated with delayed recovery.

Meijer et al. (1996) studied a cohort of 55 asthmatic children with allergy to house dust mite during and after withdrawal of inhaled corticosteroid therapy. The authors hypothesized that exogenous stimuli in the home, such as ETS, could increase circadian swings in airway diameter.

To measure this phenomenon, they examined circadian peak expiratory flow (PEF) amplitude, which is the highest daily PEF minus the lowest PEF, expressed as a percentage of the day's mean value. Compared to unexposed children, ETS exposure was associated with a greater mean PEF amplitude after discontinuation of inhaled corticosteroids (29.7 vs. 19.4, $p<0.05$). In multivariate analysis controlling for age, pet exposure, dust mite exposure, and degree of bronchial hyper-responsiveness, ETS exposure was associated with an increase in PEF amplitude ($ß = 11.2$; $p=0.001$). These results suggest that ETS exposure can increase variability in bronchial airway diameter throughout the day.

Macarthur et al. (1996) recruited 68 children in Canada who had been hospitalized twice for asthma and followed them for repeat hospitalization. Predictor data, including parental smoking, were abstracted from the inpatient medical record. Compared to unexposed children, ETS exposure was associated with a greater risk of re-hospitalization (OR 1.4; 95% CI 0.9; 2.4). Reflecting the small sample size, the confidence intervals are wide and include no effect. A serious limitation is assessment of ETS exposure based on medical record review, which may not accurately reflect exposure status in all cases. The small sample size and lack of statistical control for confounding variables also limit the conclusions that can be drawn from this study.

6.2.1.3. Summary – Asthma Exacerbation in Children

Taken together, the recent evidence supports the original 1997 Cal/EPA report's conclusion that ETS is a causal factor for asthma exacerbation among children. The cross-sectional studies are all limited by the possibility of selection effects, such as smoking reduction by parents who have children with more severe asthma. This bias, which is unavoidable in cross-sectional studies, would attenuate any observed risk estimate. The longitudinal studies, which are less prone to this bias, are most consistent with an adverse effect of ETS on childhood asthma status, and consistently show elevated risk of symptoms, more and prolonged medication use, and increased school absenteeism. In addition, as shown in a recent meta-analysis by Vork *et al.*, (2002), hidden environmental differences between studies may distort risk estimates. Specifically, higher ETS-related asthma risks were reported in areas with lower ambient air pollution. It was suggested that in polluted areas, individuals who are genetically more susceptible to asthma may be more affected by the ambient air pollution than by ETS, thus masking the effects of ETS

exposure. If nondifferential, failure to account for the effects of ambient air pollution could bias risk estimates towards unity.

6.2.2. Respiratory Infections (children)

6.2.2.1. Background

Prior to the 1997 Cal/EPA report, the role of ETS in respiratory infections in young children was extensively reviewed by the NRC (1986), Surgeon General (1986) and U.S. EPA (1992). For this reason a separate *de novo* analysis of the primary literature was not conducted at that time. Based on those reviews, the Cal/EPA report asserted the following.

> "It has been clearly established in nearly two dozen reports reviewed by the National Research Council (1986), the Surgeon General (U.S. DHHS, 1986) and the U.S. EPA (1992), that ETS exposure increases the risk of acute lower respiratory disease in young children by 1.5 to 2-fold."

> "The estimates of the magnitude of the effect of household ETS exposure on respiratory infections are remarkably consistent among the many studies that have examined this relationship. The effects are most marked in infants and toddlers, and are often not detectable in school children, who may be less exposed than younger children or who may have developed immunity against many respiratory pathogens."

6.2.2.2. New Epidemiological Findings

The more recent studies summarized in table 6.22 and the paragraphs below continue to support an elevated risk for lower respiratory infection (LRI) and reconfirm the observations of greater susceptibility at younger ages. Higher risks are observed for atopic children and children whose mothers smoked during pregnancy as well as after delivery.

Table 6.22 Respiratory Illness in Children Exposed to ETS

Reference Country	Study description	Exposure To smoke	Outcome and RR (95% CI)	Comments
Meta-analyses				
Li *et al.* 1999 Australia	Meta-analysis of 13 studies of ETS and lower respiratory tract infections (LRI). From 3 Chinese studies -	Pre/postnatal Hospitalization LRI 0-2 yrs old LRI 0-6 yrs old LRI 3-6 yrs old Postnatal only	LRI* 1.93 (1.66; 2.25) 1.71 (1.33; 2.20) 1.57 (1.28; 1.91) 1.25 (0.88; 1.78) 2.13 (1.52; 3.00)	Hospitalization for respiratory illness nearly double by ETS in infancy and early childhood. ETS associated with LRI mainly in younger kids. Postnatal-only data from Chinese studies where mothers didn't smoke.
Strachan and Cook 1997 US	Meta-analysis of 38 studies of lower respiratory infection in first 3 yrs of life.	Parental smoking Either Maternal Other	Pooled ORs 1.57 (1.42; 1.74) 1.72 (1.55; 1.91) 1.29 (1.16; 1.44)	Infection risk highest for maternal smoking. Risks also elevated if father or other household members smoked.
Original studies				
Gilliland *et al.* 2003	Absenteeism among fourth-graders related to respiratory illness. n = 1,932	Household Any ETS Maternal only Paternal only Both 1 smokers ≥ 2 smokers	Respiratory-illness-related absences 1.27 (1.04; 1.56) 1.44 (1.06; 1.94) 0.93 (0.64; 1.35) 1.80 (1.31; 2.46) 1.17 (0.92; 1.49) 1.75 (1.33; 2.30)	Children exposed to ETS had more illness-related and non-illness-related school absences than non-exposed children. Dose-dependence for both illness-related and respiratory-illness-related absences.
Lam *et al.* 2001 China	Health service usage among population-based cohort during first 18 mo. n = 8327	Mother *In utero* *In utero* Postnatal	Dr consults 1.26 (1.14; 1.39) Hospitalizations 1.18 (1.05; 1.31) 1.26 (1.00; 1.25)	Mothers exposed to ETS during pregnancy and/or after. No maternal active smoking.
Gurkan *et al.* 2000 Turkey	Association of ETS with serum cotinine and bronchiolitis in infants, 2-18 mo. n = 28	Parental smoking Cotinine Both parents Mother only	Bronchiolitis 10.8 vs 3.8 ng/ml in controls $p<0.05$ $p<0.05$	Infants with bronchiolitis had significantly higher serum cotinine ($p<0.0001$) and greater odds that one or both parents smoked.

Table 6.22 Respiratory Illness in Children Exposed to ETS

Reference Country	Study description	Exposure To smoke	Outcome and RR (95% CI)	Comments
Hajnal *et al.* 1999 Switzerland	Cross-sectional study of 6-14 yr olds and association of ETS and respiratory symptoms. n = 4470	Maternal smoking (current) Cough Respiratory infection Shortness of breath Any ETS at home Cough Respiratory infection Shortness of breath	Symptoms in last 12 months 1.36 (1.14; 1.61) 1.25 (1.06; 1.48) 1.71 (1.18; 2.48) 1.15 (0.99; 1.33) 1.19 (1.03; 1.37) 1.50 (1.08; 2.07)	Respiratory symptoms in preceding 12 months related to ETS, especially from maternal smoking. Risks higher if mother smoked in pregnancy.
Gergen *et al.*, 1998 US	Cross-sectional from NHANES III of 2 mo-5 yr olds for bronchitis or wheezing during previous 12 months. n = 7680	**2-24 mo** 1-19 cig/day ≥ 20 “ 1-19 cig/day ≥ 20 “ **3-5 yr** 1-19 cig/day ≥ 20 “ 1-19 cig/day ≥ 20 “	bronchitis 1.3 (0.8; 1.9) 2.5 (1.6; 4.1) wheezing 1.7 (1.2; 2.5) 2.7 (1.7; 4.2) bronchitis 1.2 (0.7; 2.1) 1.3 (0.6; 2.9) wheezing 1.2 (0.8; 1.8) 1.2 (0.6; 2.4)	Symptoms of respiratory illness (cough or wheezing) increased by ETS, especially at higher doses. Younger infants more susceptible than older.
Peters *et al.* 1998 Hong Kong	Healthcare usage by 8 -13 yr-olds for 3 month period for resp. symptoms n = 10,402	Household 1 smoker ≥ 2 smokers 1 smoker ≥ 2 smokers	Any symptom 1.15 (1.01; 1.31) 1.38 (1.14; 1.67) 13.1% cost incr. 24.7% “	More frequent doctor consultations if one or both parents smoke especially for cough and phlegm. P for trend <0.001 for any symptoms resulting in doctor visits.

Table 6.22 Respiratory Illness in Children Exposed to ETS

Reference Country	Study description	Exposure To smoke	Outcome and RR (95% CI)	Comments
Margolis *et al.* 1997 US	Cohort study of ETS parental smoking and urinary cotinine in infants ≤ 12 months of age. n = 325	Parent report ≤ 10 cig/day > 10 " urine cotinine ≤ 120 ng/mg > 120 "	Acute LRI 1.5 (1.1; 2.0) 2.2 (1.3; 3.8) 1.3 (0.8; 2.1) 1.4 (0.9; 2.1)	ETS by parental report increased respiratory illness but urinary cotinine only weakly associated.
Jedrychowski & Flak 1997 Poland	Cross-sectional of 9-yr olds. ETS and respiratory infections. n = 1129 Pre- and postnatal. Atopy + postnatal-only	Postnatal ≤ 9 cig/day ≥ 10 " Pre+postnatal ≤ 9 cig/day ≥ 10 " Atopy + 0 Atopy ≤ 9 Atopy ≥ 10	Diagnosed RI* 1.32 (0.83; 2.10) 1.74 (1.06; 2.87) 2.32 (1.13; 4.76) 2.36 (1.32; 4.17) 2.86 (1.61; 5.10) 3.39 (1.93; 5.93) 3.31 (1.71; 6.42)	Doctor-diagnosed respiratory infection (RI; laryngitis, tracheitis, bronchitis) risk significant at high ETS, especially if mother smoked in pregnancy or if child has atopy.
Nafstad *et al.* 1996 Norway	Prospective study: effects of breastfeeding and maternal ETS on LRI in 1-yr olds. n = 3238	Maternal breastfed 0-6 mo breastfed >6 mo breastfed 0-6mo breastfed >6 mo	Any LRI* 2.2 (1.6; 3.1) 1.1 (0.7; 1.6) Severe infection 4.6 (2.5; 8.3) 1.1 (0.5; 2.7)	LRI; bronchitis, pneumonia, bronchiolitis risk increased by ETS but effect ameliorated by prolonged breastfeeding.

RI respiratory infection; LRI lower respiratory tract infection

* LRI lower respiratory tract infection; RI respiratory infection

6.2.2.2.1. Meta-analyses

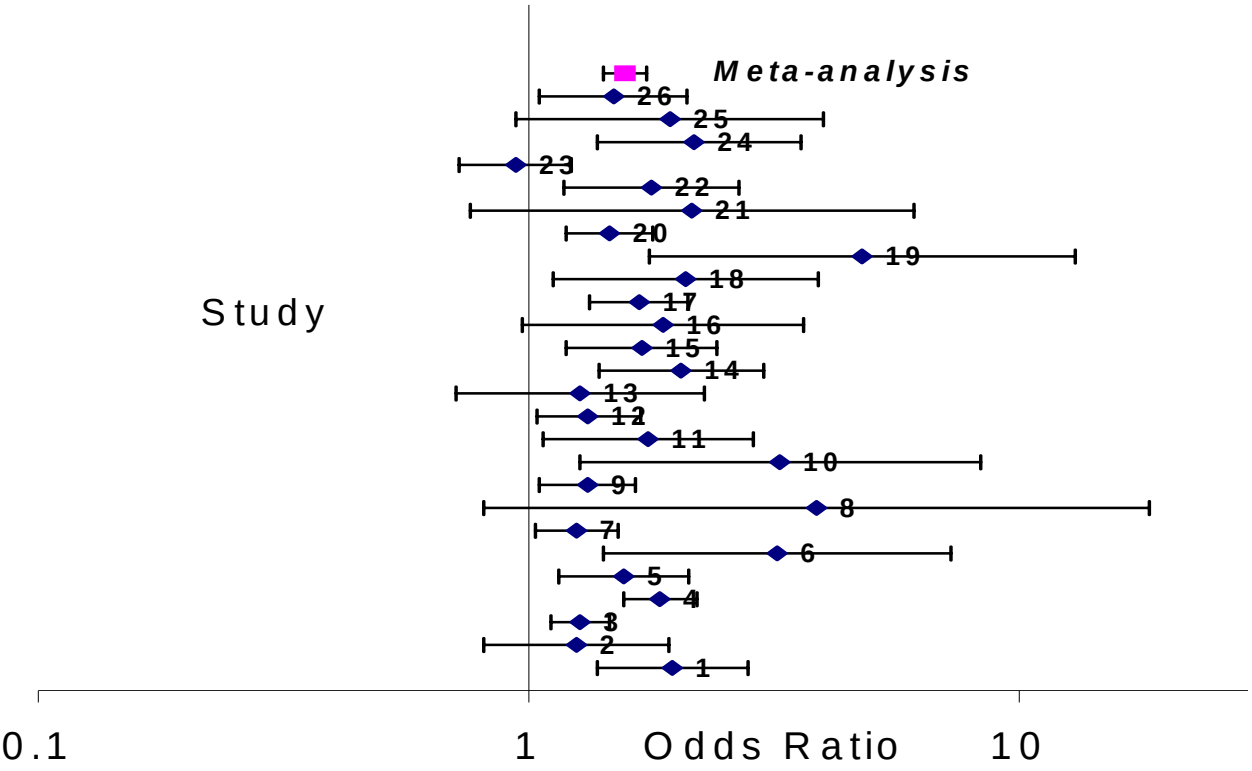
Li et al., 1999. The association between ETS exposure and lower respiratory tract infections (LRI; pneumonia, bronchitis, bronchiolitis) in childhood was also examined in a meta-analysis of thirteen studies, comprising 3 cohort, 2 case-control and 8 cross-sectional studies. The authors' criteria for inclusion in this meta-analysis included primary studies that provided information on individual level ETS exposure and serious lower respiratory tract infections or hospitalization for respiratory illness in infancy or early childhood. From seven studies it was possible to calculate an overall risk of hospitalization for respiratory illness associated with ETS exposure, resulting in an OR of 1.93 (95% CI 1.66; 2.25). When the data were categorized by age, the ORs for LRI from ETS exposure were 1.71 (95% CI 1.33; 2.20) for 0-2 yr olds, 1.57 (95% CI 1.28; 1.91) for 0-6 yr olds, and 1.25 (95% CI 0.88; 1.78) for 3-6 yr olds. While there was evidence of increased risk at all ages, after tests for heterogeneity of risk association across studies, only the risk for the 0-6 yr old group achieved statistical significance. The decrease in risk in older children is consistent with other studies. Adjustment for confounding was not uniform across studies. Sensitivity analysis of those studies adjusting for confounding resulted in a slight increase in the OR, from 1.93 to 2.05. Only three studies allowed differentiation of the effects of pre- versus postnatal smoke exposure. From these three studies, an OR of 2.13 (95% CI 1.52; 3.00) was calculated for LRI from postnatal ETS. To address possible publication bias, the authors searched for unpublished studies. Two studies were found, neither of which had sufficient data to be included in the meta-analysis but both showed a positive association between ETS and LRI. This analysis thus provides strong evidence for an association between ETS exposure and early childhood infections of the lower respiratory tract.

Strachan and Cook (1997) conducted a meta-analysis of 38 studies examining various measures of lower respiratory illness in children exposed to ETS. Studies that looked at ETS exposure and acute lower respiratory illness (LRI) in the first three years of life were included in the meta-analysis. Inclusion required that adequate information be given so that odds ratios could be determined. The studies included represent community and hospital studies as well as all study designs (case-control, cross-sectional, and longitudinal). Odds ratios were pooled using a "random effects" model that made allowances for heterogeneity of effect between studies. Ten of the studies looked at "wheeze" as the outcome measure. The other studies looked at various

combinations of acute bronchiolitis, acute bronchitis, pneumonia, and upper and lower respiratory infection.

Pooled odds ratios were 1.57 (95% CI; 1.42; 1.74) for LRI with smoking by either parent, 1.72 (95% CI; 1.55; 1.91) for maternal smoking, and 1.29 (95% CI; 1.16; 1.44) for smoking by other household members where the mother did not smoke. All but one study that compared either parent smoking with neither parent smoking showed an increased risk to children of smokers and the ninety-fifth percentile confidence intervals for the vast majority of outcome measures did not include one (Fig 6.2). While not directly evaluated in a quantitative fashion, the authors report that the associations with parental smoking were robust to adjustment for possible confounders and that most studies showed evidence of an exposure-response relationship where data were adequate to investigate this. The pooled ORs for smoking by either parent and for smoking by other household members are statistically significant and support an association of postnatal ETS with respiratory illness that is independent of maternal prenatal smoking.

Figure 6.2 Effects of Either vs Neither Parent Smoking on Respiratory Illness; Odds Ratios and 95% CI (Data from Strachan and Cook, 1997)



Study Descriptions and References

Community studies: "Lower Respiratory Illness".

1 Leeder *et al.*, 1976
2 Gardner *et al.*, 1984
3 Pedreira *et al.*, 1985
4 Ferris *et al.*, 1985
5 Fergusson & Horwood, 1985
6 McConnochie & Roghmann, 1986
7 Chen *et al.*, 1988
8 Hayes *et al.*, 1989
9 Forastiere *et al.*, 1992
10 Hakansson & Carlsson, 1992
11 Richards *et al.*, 1996

Community studies: "Wheezing Illness".

12 Fergusson & Horwood, 1985
13 Chen *et al.*, 1988
14 Burr *et al.*, 1989
15 Lucas *et al.*, 1990
16 Halken *et al.*, 1991

Community study: "Upper and Lower Respiratory Illness".

17 Ogston *et al.*, 1987

Hospital admission studies: "Lower Respiratory Illness".

18 Ekwo *et al.*, 1983
19 Hall *et al.*, 1984
20 Taylor & Wadsworth, 1987
21 Reese *et al.*, 1992
22 Jin & Rossignol, 1993
23 Victora *et al.*,1994
24 Rylander *et al.*, 1995

Hospital admission studies: "Lower and Upper Respiratory Illness".

25 Ogston *et al.*, 1985
26 Chen, 1994

6.2.2.2.2. New Epidemiological Studies

Gilliland et al., 2003. As described in section 6.1.1.2, this study examined the effects of ETS exposure on illness-related absenteeism in a cohort of 1,932 fourth-grade children in 12 California communities. Data on sociodemographics, indoor exposures and medical histories were obtained from parents or guardians via questionnaires at study entry. Attendance data were collected from the schools, and parents were contacted by telephone to determine the reason for the absence. Illness-related absences were categorized into respiratory or gastrointestinal. To estimate the risk of absenteeism associated with ETS exposure, incident absence rates were stratified and adjusted for sociodemographic variables including community, ethnicity, age, gender, parental education, health insurance, family income, BMI, and number of hours of outdoor activity.

Any ETS exposure was found to significantly increase the incidence of missed school days, including non-illness-related (RR 1.29, 95% CI 1.02; 1.63), illness-related (RR 1.33, 1.13; 1.57), and respiratory-illness-related (RR 1.27, 95% CI 1.04; 1.56) absences. Among illness-related and especially respiratory-illness-related absences, there was evidence of dose-response relationships associated with increasing numbers of smokers in the household.

Lam et al. (2001) also examined the general effects of ETS on healthcare utilization in a large prospective, population-based cohort study in China. Some 8,327 parent-infant pairs were followed for the first 18 months after birth. Health services usage was quantified as a broad measure of illness. The population was ideal for evaluating the effects of smoking by household members other than the mother since there was only a 4.6% maternal smoking rate. After adjusting for maternal education and employment, age, birth order, birth weight, delivery method and breastfeeding, ETS exposure *in utero* was associated with more outpatient consultations (OR 1.26; 95% CI 1.14; 1.39) and hospitalizations (OR 1.18; 95% CI 1.05; 1.31) in infants of nonsmoking mothers. Postnatal exposure to ETS was associated with increased hospitalization risk (OR 1.26; 95% CI 1.00; 1.25) but not with outpatient consultation usage.

Gurkan et al., 2000. In a Turkish case-control study the association between viral bronchiolitis and ETS exposure as measured by serum cotinine was examined. The study group comprised 28 infants, 2-18 months old, admitted to an emergency room with acute syncytial viral bronchiolitis, and 30 age-matched controls admitted with non-respiratory diseases. At admission, cotinine

levels were determined and data collected on health, demographics and family smoking history. Infants with bronchiolitis had significantly elevated cotinine levels compared to controls (10.8 vs 3.9 ng/ml; $p < 0.0001$) both upon admission and during the post-bronchiolitis stage ($p < 0.0001$). Compared to controls, children with bronchiolitis were significantly more likely to have one or both parents who smoked ($p < 0.05$) and, where only one parent smoked, it was more often the mother ($p<0.05$). No significant differences were found between the two groups for the social, educational, and housing measures, nor for breastfeeding; and no multivariate analysis incorporating these factors was reported. The contribution of prenatal smoking was not assessed as this study focused on recent nicotine exposure as reflected in serum cotinine, levels of which correlated well with reported parental smoking. This study found a significant association between measures of current ETS exposure and increased incidence of syncytial viral bronchiolitis.

Hajnal et al., 1999. This investigation was part of a larger cross-sectional Swiss study of the effects of air pollution on childhood allergies and respiratory infections. Data were collected by questionnaire from the parents of 4,470 children, ages 6-14 yrs, on demographics, smoking habits, history of respiratory and allergic diseases, parental education, living situation and family size. Logistic regression analyses were used to calculate ORs for respiratory symptoms adjusted for age, sex, parental education, nationality, number of siblings, family history of atopy and asthma, heating and cooking fuels, pets, farming as the family profession, and study area. Children exposed to ETS at home had a statistically significantly elevated risk of respiratory infections (OR 1.19) during the preceding 12 months which increased if the source of ETS was the mother (OR 1.25), and even more if she smoked prenatally as well (OR 1.42) (Table 6.23). Similarly, attacks of shortness of breath after exercise, and repeated cough and bronchitis during the previous 12 months were increased by ETS exposure, especially where the mother smoked prenatally and continued to smoke currently ($p<0.05$). A dose response was observed with increasing numbers of cigarettes smoked per day for respiratory infections, repeated cough, and wheezing after exercise. Paternal current smoking was less strongly associated with these symptoms.

Table 6.23 Respiratory Symptoms with ETS Exposure; Odds Ratios (from Hajnal *et al.*, 1999)

Symptoms OR (95% CI)	Any exposure at home	Maternal current	Maternal current and prenatal	Paternal current
Repeated cough /12 mo	1.15 (0.99; 1.33)	1.36 (1.14; 1.61)	1.55 (1.24; 1.93)	0.94 (0.78; 1.14)
Respiratory infection /12 mo	1.19 (1.03; 1.37)	1.25 (1.06; 1.48)	1.42 (1.14; 1.76)	1.13 (0.94; 1.36)
Bronchitis /12 mo	1.18 (0.97; 1.44)	1.25 (0.99; 1.56)	1.33 (1.01; 1.75)	1.12 (0.86; 1.44)
Shortness of breath /exercise	1.50 (1.08; 2.07)	1.71 (1.18; 2.48)	1.73 (1.10; 2.77)	1.18 (0.77; 1.83)

The strengths of this study include extensive control for various risk factors and confounders, and the apparent ability to discriminate prenatal and postnatal maternal smoking. No airborne measures of ETS exposure or biomonitoring were included. The data support an association of ETS exposure with increased respiratory infection and impaired lung function.

Gergen et al., 1998. The Third National Health and Nutrition Examination Survey (NHANES III) was the basis for this cross-sectional analysis of the contribution of ETS exposure to respiratory illness in 7,680 children, 2 months to 5 years of age. Data on demographics, education, health history, breastfeeding and smoking habits were derived from home interviews and physical examinations.

Logisitic regression analysis, adjusted for age, sex, race, birth weight, day care, history of allergy, breastfeeding, education, and household size showed that occurrence of bronchitis or three or more episodes of wheezing in the previous 12 months was associated with ETS exposure, especially at higher exposure levels. Stratification by age revealed that the youngest children (2 mo – 2 yrs) were more susceptible than were the 3-5 year olds (Table 6.24). Calculations of attributable risk from these data indicate that among children exposed to ETS from ≥ 20 cigarettes per day, 55-60% of the cases of chronic bronchitis and episodes of wheezing (3 or more per year) were attributable to ETS exposure.

Maternal smoking during pregnancy was seen to increase chronic bronchitis and episodes of wheezing, again especially in the younger children. While this study did not allow separation of pre- from postnatal exposures, the ORs for bronchitis and wheezing associated with ETS from ≥ 20 cigarettes per day were generally higher than those associated with *in utero* exposure. This

suggests that, at the very least, postnatal ETS exacerbates deteriorations in respiratory health resulting from exposure *in utero*.

Table 6.24 Age-Dependent Respiratory Symptoms with ETS; Odds Ratios

Condition # cigarettes/day	Total OR (95% CI)	2 mo-2 yrs OR (95% CI)	3-5 yrs OR (95% CI)
Bronchitis 0	1	1	1
1-19	1.2 (0.8; 1.7)	1.3 (0.8; 1.9)	1.2 (0.7; 2.1)
≥ 20	1.8 (1.1; 3.0)	2.5 (1.6; 4.1)	1.3 (0.6; 2.9)
Wheezing 0	1	1	1
1-19	1.4 (1.1; 1.9)	1.7 (1.2; 2.5)	1.2 (0.8; 1.8)
≥ 20	1.9 (1.2; 3.1)	2.7 (1.7; 4.2)	1.2 (0.6; 2.4)
In utero exposure			
Bronchitis	1.5 (1.1; 2.0)	2.2 (1.6; 3.0)	1.0 (0.6; 1.8)
Wheezing	1.8 (1.4; 2.4)	2.1 (1.5; 2.9)	1.3 (0.8; 2.0)

(Data from Gergen *et al.*, 1998)

Peters et al., 1998. One way of quantifying the health and societal impacts of ETS exposure is to compare the utilization of healthcare services and the attendant costs for children from smoking versus nonsmoking households. The frequency of doctor consultations in Hong Kong for cough, phlegm, or wheeze over a three-month period among 10,402 children ages 8-13 years was assessed by questionnaires completed by both the children and their parents. Data were collected on respiratory symptoms, doctor visits, family smoking habits, socioeconomic status, age, area of residence and educational level. In the analyses, adjustment was made for potential confounding by age, sex, district of residence, father's education, and type of housing.

Physician consultations for all symptoms were significantly more frequent among children from households with one or more smokers (Table 6.25). There was also a significant dose response trend for the cough, phlegm, and any-symptom categories related to the number of household smokers. This trend was also reflected in the estimated costs associated with the provision of healthcare. The expected healthcare costs for children from households where only one person smoked were 13.1% higher, while if two or more people smoked the costs were 24.7% higher than in nonsmoking households.

Table 6.25 Doctor Consultations for Respiratory Symptoms by Number of Smokers

Household smokers	Cough OR (95% CI)	Phlegm OR (95% CI)	Wheeze OR (95% CI)	Any symptom OR (95% CI)
None	1	1	1	1
One	1.15 (1.01; 1.32)	1.26 (1.02; 1.54)	1.04 (0.76; 1.41)	1.15 (1.01; 1.31)
Two or more	1.33 (1.08; 1.64)	1.33 (0.97; 1.83)	1.57 (1.02; 2.43)	1.38 (1.14; 1.67)
Trend by # smokers	P < 0.01	P < 0.05	NS	P < 0.001

(Data from Peters *et al.*, 1998)

Margolis et al. (1997) examined the association between the incidence of acute lower respiratory illness (LRI) and two measures of passive smoke exposure in a community-based cohort study comprising 325 infants. Data on smoking habits, demographics, environment, health history and LRI symptoms were collected during home visits at 3 weeks, and 1, 6, and 12 months of age and by telephone. Urine was collected from the infants for cotinine analysis. The relationship between ETS and LRI was examined with Poisson regression models adjusted for such factors as education, birth weight, breastfeeding, gender, history of allergy or respiratory disease, maternal age, and daycare attendance.

By both measures of ETS, increased risk of LRI was associated with increasing exposure. Although the trend was similar, a statistically significant association with LRI was observed with parents' reported smoking but not with urinary cotinine. This is similar to Rylander *et al.* (1995). The strong association between reported ETS and LRI versus the weak association with urinary cotinine is likely related to individual differences in nicotine metabolism, and suggests that other smoke components in addition to nicotine or its metabolites are responsible for the effects of ETS on respiratory disease. This is consistent with a direct versus systemic action of smoke components on the lungs.

Table 6.26Incidence and Risk of Lower Respiratory Tract Infection with ETS

Exposure	Incidence (95% CI) (episodes/child-yr)	RR (95% CI)
None	0.6 (0.30; 1.2)	- - -
≤ 10 cigarettes/day	0.89 (0.42; 1.9)	1.5 (1.1; 2.0)
> 10 "	1.3 (0.54; 3.2)	2.2 (1.3; 3.8)
Cotinine (ng/mg)		
0	0.64 (0.37; 1.1)	- - -
≤ 120	0.82 (0.41; 1.6)	1.3 (0.8; 2.1)
> 120	0.88 (1.46; 1.7)	1.4 (0.9; 2.1)

(Data from Margolis *et al.*, 1997)

Prenatal exposure data was not available for all cases but where available, the correlation between prenatal smoking with measures of ETS exposure and urinary cotinine reportedly was weak. This information was thus excluded from the analysis precluding determination of the contribution of prenatal exposure. Nevertheless, the data suggest that postnatal exposure to ETS from more than 10 cigarettes per day doubles the risk and incidence of LRI.

Jedrychowski and Flak, 1997. The effects of pre- and postnatal smoke exposure on respiratory infection were assessed in a cross-sectional study of 1,129 9-year old school children in Poland. The occurrence of doctor-diagnosed upper (tonsilitis) and lower (laryngitis, tracheolitis, bronchitis) respiratory infections (RI) during the previous 12 months was the subject of this analysis. Data regarding the mothers' smoking habits both during and after pregnancy, educational level and child's history of diagnosed allergy were collected by interview and the latter were adjusted for in the multivariate analyses.

Postnatal-only exposure to ETS was associated with increased risk of RI (OR 1.32) that was statistically significant at higher exposure levels (OR 1.74) (Table 6.27). Combined pre- and postnatal smoking more than doubled the risk of RI relative to no exposure. In the absence of prenatal exposure, there was a significant risk of RI associated with atopy (reported doctor diagnosis of allergy; OR 2.86) that was exacerbated by postnatal exposure to ETS (OR 3.39).

Table 6.27 Respiratory Infections with Atopy, Pre- and Postnatal ETS; Odds Ratios

Smoke exposure	OR (95% CI)
Postnatal only ≤ 9 cigarettes/day	1.32 (0.83; 2.10)
Postnatal only ≥ 10 "	1.74 (1.06; 2.87)
Pre- & Postnatal < 9 "	2.32 (1.13; 4.76)
Pre- & Postnatal ≥ 10 "	2.36 (1.32; 4.17)
Atopy + none	2.86 (1.61; 5.10)
Atopy + postnatal only ≤ 9 cig/day	3.39 (1.93; 5.93)
Atopy + postnatal only ≥ 10 "	3.31 (1.71; 6.42)

(Data from Jedrychowski and Flak, 1997)

This study found a strong association between postnatal ETS exposure and RI, especially at higher smoke levels, in combination with prenatal smoking and in the presence of underlying atopy. The estimation of exposure was, however, retrospective over a ten-year period and so may be subject to some recall bias. An evaluation of this smoking habit status questionnaire by

the authors (utilizing plasma cotinine at delivery) suggests that the observed risk is underestimated by the exposure misclassification error.

Nafstad et al., 1996. Based on a birth cohort in Norway, this prospective study examined the effects of breastfeeding and maternal smoking on the incidence of reported doctor-diagnosed lower respiratory tract infections (LRI; i.e. bronchitis, pneumonia, bronchiolitis) during the first year of life in 3,238 children. Data collected at birth, and at 6 and 12 months of age included parental smoking habits, duration of breastfeeding, gender, birth weight, maternal age and education, family income, family structure and health history. Logisitic regression analysis adjusted for these factors showed that in children breastfed for 0-6 months, ETS exposure from the mother carried a risk for all LRI of 2.2 (95% CI 1.6; 3.1), and for infection requiring hospitalization, an OR of 4.6 (95% CI 2.5; 8.3) compared to no smoking with breastfeeding for >6 months. The effect of ETS was ameliorated by prolonged breastfeeding, dropping the OR for all infections to 1.1 (95% CI 0.7; 1.6), and for severe infections also to 1.1 (95% CI 0.5; 2.7). It is not clear if and what other factors may have distinguished the long-term breastfeeding mother-infant pairs from those breastfeeding for less time. However it is evident that in the latter group, ETS exposure was associated with a doubling of the risk of any LRI, and a more than 4-fold increase in severe LRI requiring hospitalization.

6.2.2.3. Summary – Lower Respiratory Illness in Children

The studies reviewed provide additional strong evidence supporting the 1997 conclusion that ETS exposure is causally related to lower respiratory tract infections in children. All eleven of the studies reviewed above found increased risk of respiratory illness in children associated with smoke exposure as measured by incidence of symptoms, diagnosed disease or health services utilization. While the risk of illness was highest for children of mothers who smoked during pregnancy, from five studies in which it was possible to distinguish the effects of postnatal ETS exposure from maternal prenatal smoking, the OR for symptoms of respiratory disease ranged from 1.26 to 2.13 for postnatal ETS exposure. The effects of ETS were exacerbated if the child was atopic (OR 3.31 vs 1.74; Jedrychowski and Flak, 1997) but ameliorated somewhat in one study by breastfeeding (OR 1.1 vs 4.6; Nafstad *et al.*, 1996). As seen previously, younger children were more at risk than older children. This is thought to reflect not only maturation of the pulmonary and immune systems, but also less time spent in the presence of a household

smoker as the child matures. Maternal smoking was generally the most important source of ETS and the risk of illness increased with more intense smoking and/or additional household smokers.

6.2.3. Otitis Media in Children)

6.2.3.1. Background/Definitions

The following pathophysiological background information is reiterated from the earlier Cal/EPA report:

> "Otitis media is the most commonly diagnosed problem in outpatient pediatrics in the United States today (Greer *et al.*, 1993). In the context of this discussion, it is useful to consider the anatomy and physiology of middle ear disease before reviewing the data concerning ETS as a risk factor for otitis media. The middle ear communicates with the nasopharynx via the Eustachian tube. The Eustachian tube acts as a barrier to microorganisms originating in the pharynx, as a pressure equalization channel, and as conduit of drainage for secretions originating in the middle ear. Eustachian tube dysfunction of whatever etiology results in a sustained pressure differential between the middle ear and the surrounding atmosphere, with subsequent effusion of serous fluid into the middle ear. Alone, this condition is called "serous otitis media," and produces a sensation of fullness and temporarily decreased hearing. Should the serous fluid become infected (usually with bacteria), "acute otitis media" results, with pain, fever, and the potential for tympanic membrane (TM) perforation. Serious secondary complications (meningitis, mastoiditis) can also occur, as can a self-perpetuating cycle of acute and serous otitis media (Hackshaw *et al.*, 1997). Chronic serous effusions, with or without intervening infections, may lead to a variety of complications, including mucoid effusion (so-called "glue ear") and stretching of the tympanic membrane ("incompetent TM" or "atelectatic TM"), each resulting in more sustained hearing loss than does simple serous otitis. Tympanic membrane perforation can result, not only in hearing loss, but also in the formation of a "cholesteatoma" -- an ingrowth of squamous cells from the exterior of the TM -- which, in turn, can expand and destroy the ossicles of the middle ear. Hearing loss, whether from sustained serous otitis media, mucoid effusion, atelectatic TM, TM perforation, or ossicle destruction due to cholesteatoma, can result in communication difficulties and educational impairment in children.

6.2.3.2. Summary of Previous Findings

In its 1997 report, Cal/EPA reviewed a total of 22 reports examining a possible link between ETS exposure and otitis media (OM). Twelve of these studies had previously been reviewed by the Surgeon General's Office, and an additional 10 were added as part of Cal/EPA's review process. Ten of the 12 original studies showed significant positive associations between ETS exposure and OM, and 5 of 10 studies reviewed for the first time by Cal/EPA showed significant positive associations. Of this total of 25 studies, few were without potential methodological shortcomings. The three most convincing studies were summarized as follows:

> "The reports of both the Surgeon General and the U.S. EPA expressed concern regarding potential misclassification of exposures based solely upon historical measures. Two studies (Strachan *et al*., 1989; Etzel *et al*., 1992) used objective measures of ETS exposure (salivary and serum cotinines, respectively), and both found a statistically significant relationship between ETS exposure and outcome. Likewise, two studies (Iversen., 1985; Etzel *et al.*, 1992) employed periodic prospective screening for middle ear disease, thus eliminating differential utilization of medical services by parents as a possible confounder. Again, both of these studies found statistically significant associations between ETS exposure and middle ear disease." (Cal/EPA, 1997)

6.2.3.3. New Epidemiological Findings

Seven studies not previously reviewed by the Surgeon General's Office (U.S. DHHS, 1986), NRC (1986), US EPA (1992) or Cal/EPA (1997) are summarized in Table 6.28 and in the following paragraphs.

Table 6.28 Studies of Middle Ear Effusion (MEE) or Otitis Media (OM) vs ETS

Reference Country	Study Description	Exposure to smoke	Findings and OR (95% CI)	Comments
Ilicali *et al* 2001 Turkey	Case-control: OM in 3-8 yr olds vs urinary cotinine n = 114, Ctrl = 40	Parental	Cotinine elevated in 74% cases, 55% ctrls. OM OR 2.29 (1.08; 4.85) ($p<0.05$)	Cotinine elevated in more cases than ctrls. Age and sex but no other covariates used.
Rylander & Megevand 2000 Sweden	Cross-sectional 4-5 yr n = 304 OM, allergy, resp illness	ETS at home	1-19 cig, OR 1.04 > 20 cig, OR 1.18. CIs for both include 1.00	Control for allergies may have decreased OR for OM w/ETS
Gryczynska *et al* 1999 Poland	Unclear – purports to test ETS and OM among preschoolers	Parental	Results uninterpretable	Limited due to scant methodology and questionable analysis
Lister & Jorm 1998 Australia	Cross-sectional of kids 0-4 yr n = 4281 Respiratory illness	Parental	No significant association of smoking with OM	Limited due to no specific interview question on OM
Paradise *et al* 1997 US	Prospective cohort 2 mo to 2 yr. ETS and MEE n = 2253	ETS (home) Days MEE 1st yr.	# household smokers: 0 (18.4), 1 (22.8), 2 (25), ≥ 3 (24.8). Linear trend *P=<0.001*	Middle ear effusion (MEE). Controlled for SES, breastfeeding
Stenstrom *et al* 1993 Canada	Case-control of RAOM in kids < 5 yr old. n = 85	ETS in and outside the home.	ETS at home vs RAOM OR 2.68 (1.27; 5.65)	Recurrent acute otitis media (RAOM) increased with total adult smoking.
Owen *et al* 1993 US	Prospective cohort birth to 1 or 2 yrs. Effects of ETS on OME. n = 534	ETS from parents	Significantly greater number of days of OME during 2nd year with increasing number of cigarettes smoked	Otitis media with effusion (OME). ETS measured as packs/day from interview.

* MEE middle ear infusion; OM otitis media; OME otitis media with effusion; RAOM recurrent acute otitis media

Ilicali et al., 2001. In the only study employing biomarkers of ETS exposure, Ilicali *et al.* recruited 114 children (aged 3-8 yrs.) who had been referred to an otolaryngology clinic for tympanostomy for chronic OM. Forty controls with a similar age- and sex-distribution were recruited from among children referred to orthopedic clinic. ETS exposure was ascertained from children's urinary cotinine levels, with a pre-determined cutoff for "exposed" individuals. Aside from matching criteria, no other covariates were considered. As judged by biomarkers, ETS exposure was highly prevalent in both groups (74% in the case group and 55% in the control group). Nevertheless, the odds ratio for ETS exposure and OM was elevated at 2.29 (95% CI 1.08-4.85; $p<0.05$). A potential weakness of this study is its limited attention to covariates.

Rylander and Megevand, 2000. In another cross-sectional study, 304 preschool children (aged 4-5 yrs) were randomly recruited as they were enrolled in mandatory health screening. Sixty-five percent of parents contacted (204 of 340 initial sample) agreed to be interviewed. Primary variables included smoking habits at home of parents and other family members, parental report of frequency of ear infections, and frequency of colds and bronchitis during the previous year. Covariates included physician-diagnosed allergy, and maternal age. Day care attendance, molds in home, and pets in home were also examined as risk factors for respiratory disease. Odds ratios for ETS exposure (smoking in home) and OM were 1.04 for 1-19 cigarettes, and 1.18 for > 20 cigarettes per day, but both confidence intervals included 1.00. A potential weakness of this study is possible "over-control." Specifically, if ETS exposure is causally associated with atopy, and if atopy is associated with OM ($p<0.01$ in this study), then controlling for children's allergies would artificially deflate the odds ratios for ETS and OM.

Gryczynska et al., 1999. In an apparent cross-sectional study, Gryczynska and colleagues examined "interview questionnaires" [presumably of the parents] of 440 preschool (age >3 yrs., but upper limit not defined in paper) and 560 school-aged children (up to age 13). The study purports to show a relationship between ETS exposure and recurrent upper respiratory tract infection, including OM, among preschool children. However, as the study methodology was presented in only two sentences and the categorical analysis of data questionable, the study is essentially uninterpretable.

Lister and Jorm (1998) in a cross-sectional study, analyzed data obtained as part of Australian Bureau of Statistics National Health Survey during the period 1989-1990. 4,281 children aged 0-4 years were included. Paternal and maternal smoking, as well as total cigarettes smoked per day, were ascertained by interview. No specific questions were asked about OM; parents needed to volunteer the diagnosis as a "long-term condition." Covariates included gender, socioeconomic status, family size, and home language. No significant relationship between ETS exposure (i.e. parental smoking) and OM was found. Major limitations of the study included the lack of specific questions regarding OM, lack of specific questions regarding smoking in the home environment, the relatively limited treatment of potential confounders, and lack of biomarkers of ETS exposure.

Paradise et al., 1997. In a cohort study, Paradise *et al.* prospectively followed children less than or equal to 2 months of age who presented to participating hospital-based clinics or private pediatric practices. Of 3,663 children enrolled, 2,253 were successfully followed up until 2 yrs. of age with monthly screening for middle ear effusion (MEE), with or without acute otitis media, using pneumatic otoscopy. ETS exposure was ascertained by parental interview, and was indexed to the number of smokers in the household. Covariates included gender, race, birth weight, maternal age, maternal education, socioeconomic status, breast- vs. bottle-feeding, number of other children in household, and day care in the first year of life. The authors noted a significant trend toward more days with MEE during the first year of life as a function of reported number of smokers in the household (p value linear trend test = < .001; table 6.28). There was no significant association noted during the second year of life. Strengths of this study included cohort size and prospective screening for MEE. Weaknesses included use of a historical index of ETS exposure (reported number of smokers in a household) without biomarkers, lack of specific questions about smoking in the home environment or identification of family history of allergy or otitis media.

Stenstrom et al. (1993) recruited 85 children under age five years who were referred to a pediatric otorhinolaryngology clinic for recurrent acute otitis media (RAOM; defined as >4 episodes in 12-months) for this case-control study,. An equal number of age- and gender-matched controls (free of OM for the previous 12 months) were recruited from a pediatric ophthalmology clinic. Exposure status was ascertained by parental questionnaire, and included both the total number of cigarettes-per-day smoked by all caregivers/family members, as well as a specific history of smoking by any adult in the home. Potential confounders included family history of OM, documented atopy, prematurity, breast- vs. bottle-feeding, daycare attendance, and socioeconomic status. The authors observed a significantly elevated odds ratio for RAOM and ETS exposure (home exposure; OR=2.68; 95% CI 1.27-5.65), with a positive exposure-response gradient (total adult smoking). The strength of this study was its rigorous definition of RAOM and inclusion of potential exposures outside the home; its weakness was the use of an historical exposure index, without biomarkers.

Owen et al., 1993. For this cohort study, 698 healthy term infants were recruited from English-speaking homes at three hospital nurseries in Galveston, TX between 1984 and 1989. The

children were followed prospectively from birth to 1 yr. of age (n = 534) and birth to 2 yrs. of age (n = 435). Children were screened prospectively at 2-4 week intervals for otitis media with effusion (OME) using tympanometry, supplemented with acoustic reflectometry in a subset of visits. ETS exposure was ascertained by parental interview, and was taken as a continuous variable proportional to the total number of packs smoked per day by all adults in the household. Potential confounders controlled for in the study included sex, ethnicity, breast vs. bottle feeding, hours-per-week in group child care, and presence or absence of tympanostomy tubes. Family history of allergy and otitis media were not addressed. During second year of life (and particularly between the ages of 12 and 18 months), there was a significantly greater number of days with OME as a function of reported total number of packs-per-day smoked by household members. A strength of this study was the prospective nature of otitis media screening. A weakness was the use of total packs-per-day of adult smoking rather than either a more specific history of in-home smoking, or use of a smoke exposure biomarker. Potential ETS exposure outside of the home was also not documented.

6.2.3.4. Biological Plausibility

In its 1997 report, Cal/EPA highlighted at least four potential mechanisms whereby ETS exposure might predispose children to the development of middle ear disease. Eustachian tube dysfunction (ETD) plays a central role in each of these mechanisms. Newer pathophysiological data pertaining to these mechanisms are reviewed here. In addition, two new studies, one involving an animal model of secretory OM and the other an *in vitro* study of mucous hypersecretion, are included in separate categories:

1) Decreased mucociliary clearance: No new data encountered

2) Decreased Eustachian tube patency due to adenoidal hyperplasia: No new data encountered

3) Decreased patency due to ETS-induced mucosal swelling

   Vinke et al. (1999) examined nasal biopsy material obtained from the inferior turbinates of children referred for tonsillectomy-adenoidectomy. In general, children underwent surgery because of recurrent upper respiratory tract infections, sleep apnea, or recurrent

otitis media. From an initial group of 54 children screened for allergies using an in vitro test (radioimmunoassay), 10 non-atopic ETS-exposed children aged 1.4-10 years were identified, along with a like number of gender- and age-matched controls. Using immunohistochemical staining techniques, the authors found a significantly greater density of IgE-positive eosinophils (consistent with allergic inflammation) but not mast cells (indicative of allergic sensitization) in the mucosae of ETS-exposed children. They interpreted this to show a link between parentally reported ETS exposure and allergic-like inflammation in the nasal mucosa, in the absence of true allergic sensitization.

Zavras et al. (1997) conducted a cross-sectional study of 54 children age 7-12 years recruited from a pediatric dentistry clinic at a major university. Parents completed a questionnaire (including information on children's allergies and/or asthma and ETS exposure at home) and children underwent acoustic rhinometry (to determine nasal volume and minimum nasal cross-sectional area). Roughly half of the children were ETS-exposed at home per parental report, and this subgroup had significantly lower nasal volumes, correcting for age, gender, race, obesity, and allergies. Although minimum cross-sectional area was lower among ETS-exposed children, it was not significantly so. The authors interpreted their findings to indicate that ETS exposure is associated with nasal mucosal swelling, along with possible inflammation, although the latter endpoint was not directly assessed.

4) Decreased patency and impaired mucociliary clearance secondary to increased frequency of viral upper respiratory tract infections (URI's): No new data encountered

5) Animal model of secretory OM

Coggins et al. (1997) exposed male Sprague-Dawley rats to aged and diluted sidestream tobacco smoke (STS), 6 hrs/day for 5 days. Three groups of 20 animals each were exposed to: 1) high-level STS; 2) low-level STS; and 3) control conditions. Ten of 20 rats in each group were pre-treated with cold air per external auditory canal to induce middle ear effusions, and rates of clearance, rather than induction of ear pathology, were observed in these groups. Animals were examined daily for secretory otitis media (SOM), and at the conclusion of the experiment the animals were sacrificed and their

middle ears and Eustachian tubes examined histologically. Other than on the first day of exposure (when there were more incident cases of SOM in the low-exposure group than either control or high-exposure group), the rates of new-onset SOM (and rates of clearance of cold-air induced SOM) were not significantly different among the three treatment groups. Histological staining revealed no difference in the relative number of goblet cells between the three groups, nor were inflammatory cells observed. A potential limitation in interpreting this study is the fact that the rat nasal cavity much more efficiently clears water-soluble air pollutants before they can reach the pharynx (and Eustachian tube opening) than does the human nasal cavity.

6) Cell culture model of mucous hypersecretion

Borchers et al. (1999) exposed human lung carcinoma cells *in vitro* to acrolein, an irritant found in ETS. The cells produced significantly elevated levels of messenger RNA coding for two different mucins, MUC5AC and MUC5B. Mucins are an essential component of airway mucus, and the authors make the point that increased mucin production by airway epithelial cells translates clinically into mucous hypersecretion, as seen in various pathological respiratory tract conditions including asthma.

6.2.3.5. Summary and Conclusions – Otitis Media.

Of the additional seven studies reviewed here, four (all cohort or case-control studies) found a significant positive association between ETS exposure and OM. The two cohort studies (Owen *et al.*, 1993; Paradise *et al.*, 1997) both employed regular prospective screening for otitis media, using pneumatic otoscopy and/or tympanometry. (This design feature is important in eliminating the factor of "diagnostic bias" as a potential study limitation.) One of the two case-control studies utilized urinary cotinine as a marker of exposure (Ilicali, 2001). (Use of biomarkers is important in addressing the issue of potential exposure misclassification.) None of the newly reviewed studies used both prospective screening for OM *and* biomarkers, as was the case in the study by Etzel *et al.* (1992) which was reviewed in our 1997 document. Of the three remaining studies, one (Gryczynska *et al.*, 1999) was of unknown study design, and was generally uninterpretable. The remaining two "negative" studies were both cross-sectional. A major limitation of one of these studies is that it required that parents *volunteer* a diagnosis otitis media

under the general rubric of "recent or chronic respiratory illnesses" (Lister and Jorm, 1998); the other was marred by possible overcontrol (for allergy status) (Rylander and Megevand, 2000). There is, in the literature reviewed, inadequate information to draw any conclusion regarding potentially susceptible subpopulations such as children with atopy or allergy.

In 1997, Cal/EPA concluded:

> "Overall, the epidemiological data strongly support a relationship between ETS exposure in the home and either acute otitis media with effusion or serous otitis media (middle ear effusion without acute infection), particularly among children under two years of age. Limitations of available data on the chronicity of physical findings, as well as the differing patterns of recruitment in the various studies, make it impossible to distinguish separate relationships between ETS exposure and acute serous otitis media, chronic serous otitis media, and acute infectious otitis media."

The current literature review provides no compelling evidence for modifying the above conclusions regarding the association of otitis media with effusion with ETS exposure in young children. Thus, the 1997 conclusion is still appropriate and consistent with the additional newer data.

6.2.3.6. Attributable Risk Considerations

In its 1997 report, Cal/EPA estimated that some 134,251 pediatric outpatient visits for middle ear disease (95% CI: 78,615-188,676) could be attributed to ETS exposure in the home. Given the interval decrease in estimated adult smoking rates in California, as well as the intervening change in population, the following re-calculation is offered:

1) According to the California Department of Health Services Tobacco Control Section an estimated 11.4% of California children under the age of 18 years were exposed to ETS in the home in 1999 (Gilpin *et al.*, 2001). This compares with an earlier estimate of 33% of children under 3 years (Tariq *et al.*, 2000), used in Cal/EPA's 1997 calculations.

2) Using data from Etzel *et al.* (1992) indicating that ETS-exposed children under age 3 years experience an average of 38% (95% confidence interval, 21-56%) excess incidence

of OM (Relative risk – 1; R-1), we applied California's estimated ETS exposure prevalence (p) of 11.4 % to obtain an ETS-attributable otitis media fraction (a) of 4.1% (95% confidence interval, 2.5-6.4%).

$$a = p\,(R-1) / (p(R-1) +1)$$ (Lilienfeld and Lilienfeld, 1980

3) Data from the National Ambulatory Medical Care Survey (NAMCS) indicates that otitis media is the most common outpatient pediatric diagnosis nationwide (accounting for approximately 18% of all office visits for children under age 5 years). OM was cited as the principal diagnosis for 102 office visits per 100 children (under two years of age) per year in 1990; and for 48 office visits per 100 children aged 2-5 years (Schappert, 1992).

4) In 2000, California had a population of 1,459,066 children under age three years. Of these children, 483,143 were under age one year, 486,587 were 1-2 years, and 489,336 were in their third year of life (U.S. Department of Commerce, 2002).

5) Assuming that ETS-related otitis media with effusion episodes generate the same number of total (initial + follow-up) visits as do non-ETS related episodes, one can combine Etzel's data (pertaining to incident cases of otitis media with effusion) and the NAMCS data (pertaining to all OM-related office visits-- both initial, follow-up, acute and chronic). This calculation of attributable risk may represent an underestimate, since ETS usually constitutes an ongoing insult to normal Eustachian tube function, in contrast to such events as viral upper respiratory tract infections. It may represent an over-estimation if a higher percentage of non-ETS related episodes result in acute otitis media which may be more likely to result in physician visits.

Combining the above data, one obtains an estimate of 50,184 office visits per year among California children under age three years for ETS-attributable otitis media episodes:

Table 6.29 ETS-attributable Office Visits for Otitis Media

	Population at risk x	Age-specific Otitis Media visit rate =	OM-Related Office visits x	ETS-attributable fraction =	ETS-attributable visits/year
Age ≤ 2 yr	969,730 x	102/100 =	989,125		
Age 2-3 yr	489,336 x	48/100 =	234,881		
			1,224,006 x	0.041 =	50,184

According to this and earlier estimates, some 84,000 pediatric physician office visits per year for otitis media may have been avoided by virtue of changes in smoking behavior on the part of California adults since the calculation in the 1997 document (based on smoking data from Wiley, 1991).

6.3. Chronic Health Effects (Children)

6.3.1. Chronic Respiratory Symptoms (children)

The previous review (Cal EPA, 1997) identified several studies addressing the occurrence of chronic respiratory symptoms in children, and concluded that these:

> "… support the conclusion, also stated in the reports by the NRC, the Surgeon General, and the U.S. EPA, that there is sufficient evidence that ETS exposure at home is causally associated with chronic respiratory symptoms (cough, phlegm, or wheezing) in children, particularly infants and young children.

Although several new studies of acute effects were discussed earlier (Section 6.1.2), no new studies addressing the chronic endpoints discussed in this section of the previous review were identified, so this conclusion is unmodified.

6.3.2. Asthma Induction in Children

Numerous studies have evaluated the impact of ETS exposure on childhood asthma induction (Chilmonczyk *et al.*, 1993). The 1997 Cal/EPA report included a meta-analysis of 37 studies conducted between 1975 and 1995 that evaluated ETS exposure as a risk factor for induction of childhood asthma. The pooled RR for asthma was 1.44 (95% CI 1.27; 1.64). These data supported a causal association between ETS and new onset of childhood asthma cases (Cal EPA, 1997). Recent studies, including an updated meta-analysis by OEHHA (submitted for publication and abstract included below), continue to support a causal role of ETS in childhood asthma

induction. The studies are presented below and in Tables 6.30 – 6.32. They are separated by study type: cross-sectional, case-control, and prospective cohort.

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Gilliland *et al* 2001 US	Cross-sectional study 4-12th graders n = 5,762	Parental smoking Postnatal only *In utero* only Both 1 smoker ≥ 2 smokers	Diagnosed asthma 1.1 (0.9; 1.4) 1.8 (1.1; 2.9) 1.4 (0.9; 2.3) 0.9 (0.6; 1.3) 1.7 (1.1; 2.5)	Asthma increased by *in utero* exposure and increasing numbers of smokers postnatally but postnatal effect included unity.
Mannino *et al* 2001 NHANES III US	Cross-sectional study Cotinine and asthma in 1,533 4-6 yr; 2,225 7-11 yr; 1,642 12-16 yr	Serum cotinine Highest tertile	Asthma OR Ever 2.3 (1.1; 5.1) Current 5.3 (2.2; 12.7) Wheeze 3.8 (1.7; 8.3)	ETS associated with asthma onset in 4-6 yr olds. Less clear risk in older kids.
Lanphear *et al* 2001 NHANES III	Cross-sectional study Asthma onset <6 yrs, n = 8257	Parental smoking Home – pre- and postnatal	Asthma OR for pre- and postnatal ETS 1.7 (1.2; 2.5)	No relation between only pre- or only post-natal ETS and asthma
Kivity *et al* 2001 Israel	Cross-sectional study Prevalence 8-17 yr n = 1243	Town - parent Arab: father Jewish: father Jewish: mother	Asthma; ETS vs none 11.4% vs 6.6% p<0.05 19% vs 11% “ 20% vs 12% “	Parental smoking significantly increased asthma prevalence.
Al-Dawood 2001 Saudi Arabia	Cross-sectional study Boys 6-15 yrs n = 1,482	Parental smoking Mother Father	Asthma 1.32 p < 0.01 1.52 p < 0.01	Asthmatic children more likely to have smoking mothers (7.8% vs 3.8%), fathers (53.9% vs 30%)
Gupta *et al* 2001 India	Cross-sectional study 6-12th graders n = 9,090	Child report Home or none	Asthma symptoms 1.8 (1.3; 2.4)	Child self-reported symptoms increased with parental smoking
Lam *et al* 1999 Hong Kong	Population-based Cross-sectional study 7-13 yrs n = 3,964	Home Any ETS 1 smoker 2 smokers ≥ 3 smokers	Asthma 0.92 (0.71; 1.19) 0.93 (CI not given) 0.97 “ 0.74 “	ETS and asthma not significantly correlated but cough, phlegm production, and recent physician visits for wheeze were elevated.
Wang *et al* 1999 Taiwan	Cross-sectional study Prevalence 11-16 yr n = 165,173	Parental smoking	Asthma OR 1.08 (1.05; 1.12)	Large, well-controlled population-based study

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Hajnal *et al* 1999 Switzerland	Population-based cross-sectional study 6-7 yr, 9-11 yr, 13-14 yr n = 4,470	Parental smoking Mother Others Any Mother Others Any Mother Others Any	Asthma 1.16 (0.89; 1.55) 1.20 (0.87; 1.65) 1.20 (0.94; 1.54) Wheeze - past 12 mo 1.36 (1.03; 1.60) 1.12 (0.81; 1.55) 1.27 (0.99; 1.63) Short breath after exercise – past 12 mo 1.71 (1.18; 2.48) 1.18 (0.77; 1.83) 1.50 (1.08; 2.07)	Multicenter study. Wheeze and attacks of shortness of breath after exercise more strongly associated with ETS (esp. maternal) than asthma.
Ronmark *et al* 1999 Sweden	Cross-sectional study Ever asthma, atopy 7-8 yr n = 2454	Maternal smoking Atopic asthma Nonatopic asthma	1.29 (0.95; 1.74) 1.17 (0.68; 2.01) 1.67 (1.04; 2.68)	ETS increased risk of asthma; ameliorated by breast-feeding. In families without history of asthma, and breast-fed < 3 months, OR for maternal smoking 1.95 (95% CI 1.18; 3.24)
Shamssain & Shamsian 1999 UK	Population-based Cross-sectional study 6-7 yr n = 3000	Family ETS Father Mother	Ever asthma 1.10 (0.84; 1.44) 1.39 (1.12; 1.74)	Maternal ETS assoc. with asthma. Ever wheezing associated with maternal: 1.46 (1.19; 1.79) and paternal:1.38 (1.11;1.72)
Gergen *et al* 1998 NHANES III	Cross-sectional study Asthma 2 mo-5 yr n = 7,680	Household 1-19 cig/day ≥ 20 “	Ever asthma 1.1 (0.8 ; 1.6) 2.1 (1.4 ; 3.2)	Physician-diagnosed asthma significantly elevated at higher exposures.
Lister & Jorm 1998 Australia	Cross-sectional study 0-4 yrs n = 4,281	Parental smoking Mother Father	Asthma 1.52 (1.19; 1.94) 0.77 (0.60; 0.98)	Maternal but not paternal smoking associated with asthma.

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Lam *et al* 1998 Hong Kong	Population-based Cross-sectional study 12-15 yrs n = 6,304	Self report home 1 smoker 2 smokers ≥ 3 smokers Father Mother	Physician diagnosed asthma 0.89 (0.69; 1.12) 0.89 (0.6; 1.32) 1.49 (0.81; 2.71) 0.92 (0.72; 1.17) 1.32 (0.71; 2.45)	Self reported physician-diagnosed asthma. Highest exposure also associated with recent use of asthma medicine OR 2.86; 95% CI 1.09 - 7.49
Kendirli *et al* 1998 Turkey	Population-based cross-sectional study 6-14 yr n = 2,334	Household parent reported	Physician diagnosed asthma 1.41 (1.16; 1.72)	Domestic ETS exposure was also associated with rhinoconjunctivitis and wheezing.
Maier *et al* 1997 US	Cross-sectional study Onset 5-9 yr n = 925	Parental smoking Home: any ETS Occasional ETS	Asthma 1.6 (0.9; 2.7) Wheeze 1.8 (1.0; 3.2) Asthma 2.5 (1.5; 4.3) Wheeze 1.8 (1.0; 3.2)	Diagnosed asthma and wheeze increased with increased ETS
Hu *et al* 1997a US	Cross-sectional study 5th graders n = 705	Parental smoking Past week *In utero*	Diagnosed asthma 0.8 (0.5; 1.5) 1.9 (1.1; 3.5)	No association of ETS in past week with asthma. Result biased by short assessment period and maternal reporting bias.
Farber *et al* 1997 US	Cross-sectional study over 3 yrs 5-17 yr n=3,174	Parental smoking 1984-5 1987-8 1992-4	Asthma 1.35 (1.01; 1.81) 1.51 (1.17; 1.96) 1.39 (1.11; 1.72)	Consistent association of asthma with maternal smoking over 10 yrs.
Selcuk *et al* 1997 Turkey	Cross-sectional study 7-12 yr n = 5,412	Home	Lifetime asthma 1.35 (1.12; 1.62) Current asthma 1.28 (0.94; 1.75)	Lifetime asthma more strongly associated with ETS than current asthma.
Cunningham *et al* 1996 US, Canada	Cross-sectional study School-based Effects of home current or previous ETS on respiratory symptoms	Maternal report Home current Home previous	Diagnosed asthma 1.08 Wheeze w/ cold 1.65 Wheeze no cold 1.15 Persistent wheeze 1.42 Diagnosed asthma 1.03 Wheeze w/ cold 1.24 Wheeze no cold 1.0 Persistent wheeze 1.03	No statistical association between current or previous ETS and "active asthma". However prenatal exposure raised risk of active asthma OR 2.7 (1.13; 6.45). Statistically significant associations were found for several wheezing outcomes.

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Chen *et al* 1996 Canada	Cross-sectional study 6-17 yrs n = 892	Parental smoking. allergic children non-allergic 1-19 cig/day ≥ 20	Diagnosed asthma 1.04 (0.49; 2.21) 2.47 (0.74; 7.86) 3.96 (1.01; 15.42) 4.58 (1.34; 15.68)	Statistically non-significant effect when stratified by allergy status but significant effect by exposure level.
Peters *et al* 1996 Hong Kong	Cross-sectional study 8-12 yrs n = 3,521	Parental smoking 1 smoker ≥ 2 smokers	Asthma symptoms 0.91 (0.69; 1.19) 1.55 (1.08; 2.23)	Exposure-response seen for asthma symptoms especially with wheeze.
Beckett *et al* 1996 US	Cross-sectional study < 18 yr n = 9,276	Parental smoking Maternal	Diagnosed asthma 1.53 (1.31; 1.80)	Race/ethnicity differences in asthma susceptibility
Stoddard & Miller 1995 US	Cross-sectional study < 18 yrs n = 7,578	Parental smoking Mother Father	Asthma last 12 mo 1.36 (1.14; 1.62) 0.83 (0.67; 1.02)	Risk fr maternal smoke greatest for young kids; decreases with age. Maternal smoking (0-2 yr) OR 1.9 (95% 1.23; 2.94).

Gilliland et al., 2001. A cross-sectional analysis of 5,762 children who participated in the Children's Health Study in Southern California evaluated the impact of *in utero* and postnatal ETS exposure on the risk of asthma. Current parent-reported smoking in the home, in the absence of previous *in utero* exposure, was not associated with the risk of reported physician-diagnosed asthma (OR 1.1; 95% CI 0.9; 1.4). In contrast, exposure to maternal smoking *in utero* was related to a greater risk of asthma (OR 1.8; 95% CI 1.1; 2.9). There was no evidence of effect modification by sex or family history of asthma or atopy. "Active asthma," which was defined as physician-diagnosed asthma with asthma-related symptoms or illnesses during the past 12 months, was also examined. There was no apparent relation between postnatal ETS exposure and the risk of active asthma (OR 1.1; 95% CI 0.8; 1.4). However, there was evidence of an exposure-response relationship between number of current smokers and the likelihood of current asthma: 1 smoker (OR 0.9; 95% CI 0.6; 1.3) and 2 or more smokers (OR 1.7; 95% CI 1.1; 2.5) (p for trend = 0.073). There was also a suggestion that combined maternal and paternal current smoking was associated with active asthma (OR 1.4; 95% CI 0.9; 2.3).

Mannino et al., 2001. Another cross-sectional study, using data from 13,944 non-smoking children who participated in NHANES III, evaluated the relationship between serum cotinine level and asthma. Among children 4-6 years old, the highest cotinine tertile was associated with a greater risk of ever and current asthma (OR 2.3; 95% CI 1.1; 5.1 and OR 5.3; 95% CI 2.2; 12.7, respectively). The highest cotinine tertile was also related to a greater risk of frequent wheezing (OR 3.8; 95% CI 1.7; 8.3) and wheezing apart from colds during the past year (OR 4.8; 95% CI 2.4; 9.9). Among older children, the impact of ETS exposure on the risk of asthma was less clear.

Lanphear et al., 2001. In a related report using an overlapping sample, other investigators evaluated child NHANES III participants who were younger than 6 years old. This analysis also used parent-reported household smoking, rather than a biomarker of ETS exposure. Parent-reported household smoking during both the prenatal and postnatal periods was associated with a greater risk of ever receiving a physician-diagnosis of asthma (OR 1.7; 95% CI 1.2; 2.5). There was no relation between prenatal only or postnatal only exposure and asthma. Because serum

cotinine is a more accurate measure of recent ETS exposure, the results reported by Mannino and colleagues (Mannino *et al.*, 2001) may provide better risk estimates.

Kivity et al., 2001. A study from Israel evaluated the prevalence of asthma among 585 children who resided in a Jewish town and 658 children who lived in a neighboring Arab town. In both towns, paternal smoking was associated with the risk of asthma. In the Arab town, the prevalence of asthma was higher among children whose fathers smoked (11.4% vs. 6.6%, $p < 0.05$). Smoking was rare among Arab mothers (2%). In the Jewish town, the prevalence of asthma was also higher among children with smoking fathers (19% vs. 11%) or mothers (20% vs. 12%) ($p < 0.05$).

Al-Dawood, 2001. This population-based cross-sectional study from Saudi Arabia evaluated 1482 boys aged 6-15 years. Based on parent survey responses, asthma was defined as reported ever wheezing, attacks of shortness of breath with wheezing, and normal breathing between attacks. Compared to non-asthmatic children, children with asthma were more likely to have smoking mothers (7.8% vs. 3.8%) and fathers (53.9% vs. 30%, $p < 0.05$ in both cases). In multivariate analysis controlling for respiratory symptoms, parental asthma status, eczema, and pets in the home, maternal and paternal smoking were also associated with asthma (OR 1.32 and 1.52, $p < 0.01$ in both cases).

Gupta et al. (2001) conducted a cross-sectional study focused on 9090 children in grades 6-12 in Chandigarh, India. Based on their written survey responses, children were classified as ETS exposed or unexposed at home (smoking parents or other family members). Asthma was defined as self-reported asthma plus recent wheezing or chest tightness. ETS exposure was associated with a greater risk of asthma, controlling for age and sex (OR 1.8; 95% CI 1.3; 2.4).

Lam et al. (1999) examined a population-based sample of 3964 younger schoolchildren aged 7-13 years. Nearly half of children (47%) indicated a smoking adult at home. There was no statistical association between passive smoking and the risk of self-reported physician-diagnosed asthma (OR 0.92; 95% CI 0.71; 1.19). There was also no apparent exposure-response relationship between number of household smokers and the risk of asthma. ETS exposure was, however, associated with a greater risk of other respiratory complaints, such as cough, phlegm production, and recent physician visits for wheeze.

Wang et al., 1999. A population-based cross-sectional study from Taiwan surveyed 165,173 children and their parents. Asthma was defined based on children's responses to a video interview developed by the International Study of Asthma and Allergies in Childhood (ISAAC), which depicts children with wheezing and other respiratory symptoms. ETS exposure at home was associated with a greater risk of asthma OR 1.08 (95% CI 1.05; 1.12). The analysis controlled for area of residence, demographic factors, personal smoking, and other covariates.

Hajnal et al., 1999. A population-based study from Switzerland evaluated 4470 children aged 6-14 years who resided in 10 different communities that represented varying levels of urbanization, climate, and air pollution. Any household ETS exposure was associated with a greater risk of parent-reported childhood asthma (OR 1.20; 95% CI 0.94; 1.54). The confidence interval, however, did not exclude no relationship. When the authors examined maternal and paternal smoking separately, paternal smoking was not associated with any respiratory symptom. In contrast, maternal smoking was related to poorer respiratory health, including a greater risk of symptoms that suggest asthma during the past 12 months: attacks of shortness of breath after exercise (OR 1.71; 95% CI 1.18; 2.48) and wheezing (OR 1.36; 95% CI 1.03; 1.80). There was a suggestion that children whose mothers smoked were more likely to suffer from recent wheezing after exercise (OR 1.32; 95% CI 0.96; 1.81). High level ETS exposure, as defined as 20 or more cigarettes per day, was associated with a greater risk of exertional wheezing (OR 1.71; 95% CI 0.91; 3.22). Taken together, these findings suggest that household ETS exposure is related to asthma and related respiratory symptoms.

Ronmark et al., 1999. Researchers from Sweden evaluated the impact of ETS exposure on childhood asthma in a sample of 2,454 children aged 7-8 years. Asthma was defined based on a combination of respiratory symptoms and parent-reported physician diagnosed asthma. In a multivariate analysis controlling for gender, family history of asthma, home dampness, pets at home, geographic location, and breast-feeding history, current maternal smoking was associated with a greater risk of ever having asthma (OR 1.29; 95% CI 0.95; 1.74). In families without a family history of asthma and who breastfed less than 3 months, the 95% CI for maternal smoking excluded no effect (OR 1.95; 95% CI 1.18-3.24). While exposure to ETS increased the risk of asthma, this was ameliorated by breastfeeding for greater than 3 months. Further analysis evaluated the impact of ETS exposure on atopic asthma, which was defined as asthma plus one

or more positive skin tests to common aeroallergens. The effect estimate for ETS was greater for non-atopic (OR 1.67; 95% CI 1.04; 2.68) than atopic asthma (OR 1.17; 95% CI 0.68; 2.01).

Shamssain and Shamsian, 1999. This cross-sectional survey of parents of 6-7 year olds from northeast England found that maternal smoking was associated with a higher risk of ever having asthma (OR 1.39; 95% CI 1.12; 1.74). There was no statistical impact of paternal smoking on asthma history (OR 1.10; 95% CI 0.84; 1.44). Both maternal and paternal smoking were related to a greater risk of ever wheezing (OR 1.46; 95% CI 1.19; 1.79 and OR 1.38; 95% CI 1.11; 1.72, respectively).

Gergen et al., 1998. Other investigators studied a similar sample of children aged 2 months to 5 years who participated in NHANES III. In this report, intensity of household smoking was evaluated in more detail, with categories for no smoking in the home, 1-19 cigarettes smoked per day, and 20 or more cigarettes smoked per day. Compared to the unexposed group, the risk of parent-reported physician-diagnosed asthma was greater in the highest exposure group (OR 2.1; 95% CI 1.4; 3.2). This elevated risk was similar in the younger (2 months-2 years) and older (3-5 years) age strata.

Lister and Jorm, 1998. In a population-based sample of Australian children aged 0-4 years, Lister and colleagues examined ETS exposure as a risk factor for asthma. Maternal smoking, but not paternal smoking, was associated with a greater risk of childhood asthma (OR 1.52; 95% CI 1.19; 1.94 and OR 0.77; 95% CI 0.60; 0.98, respectively). When the outcome variable was redefined as asthma or wheezing, the results were very similar.

Lam et al., 1998. A school-based cross-sectional study from Hong Kong examined the relation between self-reported household ETS exposure and the risk of self-reported physician diagnosed asthma among 6304 students aged 12-15 years. Residence with three or more smokers was associated with a greater risk of current asthma, although the confidence interval does not exclude no relationship (OR for living with 3 smokers vs. none 1.49; 95% CI 0.81; 2.71). The highest level domestic ETS exposure group had a higher risk of recent asthma medication use during the past two days (OR 2.86; 95% CI 1.09; 7.49). The risk estimates for asthma were higher for maternal than paternal smoking (OR 1.32; 95% CI 0.71; 2.45 and OR 0.92; 95% CI 0.72; 1.17).

Kendirli et al., 1998. Another population-based cross-sectional study from Adana, Turkey, examined 2650 children aged 6 to 14 years. As in the other study from Turkey, household smoking was related to a greater risk of parent-reported physician-diagnosed asthma (OR 1.41; 95% CI 1.16; 1.72). Domestic ETS exposure was also associated with rhinoconjunctivitis and wheezing.

Maier et al., 1997. This cross-sectional study evaluated 925 children aged 5-9 years who were recruited from schools in Seattle, Washington. Parental report of smokers in the home was associated with a greater risk of reported physician-diagnosed asthma (OR 1.6; 95% CI 0.9; 2.7) and current wheezing in their children (OR 1.8; 95% CI 1.0; 3.2), after controlling for sociodemographic covariates. When ETS exposure was defined as occasional or more smoking in the home, the impact of ETS was greater on physician-diagnosed asthma and current wheezing (OR 2.5; 95% CI 1.5; 4.3 and OR 1.8; 95% CI 1.0; 3.2). Additional analysis, which controlled for other indoor environmental exposures such as fireplace use, stove use, or dampness, did not reduce the calculated risk estimates.

Hu et al., 1997a. A cross-sectional survey focused on predominately African-American fifth grade children in Chicago. Smoking during pregnancy was related to a higher risk of asthma (OR 1.9; 95% CI 1.1; 3.5). Maternal smoking during the past week was not associated with ever having a physician diagnosis of asthma (OR 0.8; 95% CI 0.5; 1.5). However, the evaluation of smoking during the past week, as opposed to a longer or average time period, could have biased this result (but not the pregnancy related findings). If mothers with actively wheezing children were less likely to recently smoke (or report smoking), the risk estimate would be biased toward the null. In fact, mothers of children who had wheezing during the past 12 months were less likely to report recent smoking.

Farber et al., 1997. Investigators recruited a population-based sample of 3174 children aged 5-17 years who resided in a semi-rural, biracial community (African-American and white). Maternal smoking was associated with a greater risk of parent-reported childhood asthma during three successive cross-sectional surveys of the population: 1984-5 (OR 1.35; 95% CI 1.01; 1.81), 1987-8 (OR 1.51; 95% CI 1.17; 1.96), and 1992-4 (OR 1.39; 95% CI 1.11; 1.72). The

consistency of findings over a ten-year period supports the link between ETS exposure and childhood asthma.

Selcuk et al., 1997. A cross-sectional population-based study from Edirne, Turkey evaluated 5,412 children aged 7 to 12 years. Passive smoking in the household was associated with a greater lifetime history of parent-reported childhood asthma (OR 1.35; 95% CI 1.12; 1.62) and current asthma (1.28; 95% CI 0.94; 1.75).

Cunningham et al., 1996. This school-based cross-sectional study of 11,534 children living in the U.S. or Canada evaluated the relationship between maternal reports of smoking in the home and respiratory status. "Active diagnosed asthma" was defined as reported diagnosis of asthma plus respiratory symptoms or asthma medication use during the past year. There was no statistical association between any current (OR 1.08) or previous home ETS exposure (OR 1.03) and the risk of active asthma. In contrast, exposure to maternal smoking during pregnancy was associated with a greater risk of active diagnosed asthma (OR 2.7; 95% CI 1.13; 6.45). Current and previous home ETS exposure were both associated with a greater risk of several wheezing outcomes, including wheezing with colds [OR 1.65 (95% CI 1.45; 1.88) and OR 1.24 (95% CI 1.05; 1.45), respectively; $p<0.05$]. Current ETS exposure was also related to a higher likelihood of persistent wheeze (OR 1.42), dyspnea with wheeze (OR 1.35), wheeze with exercise (OR 1.24), medication for wheeze (OR 1.23), and emergency department visit for wheeze (OR 1.63) ($p<0.05$ in all cases). For all wheezing outcomes, there was evidence of an exposure-response relationship for number of cigarettes smoked per day in the home.

Chen et al., 1996. A population-based cross-sectional study from Saskatchewan, Canada, evaluated 892 children aged 6-17 years. Asthma was defined as parental report that the child had ever been diagnosed with asthma by a physician. The analysis was stratified by childhood allergy status, which included reported allergy to food, inhaled allergens, skin allergy, or other allergy. Among children with any reported allergy, there was no apparent relation between parent or other household member smoking and the risk of ever having asthma (OR 1.04; 95% CI 0.49; 2.21). In the non-allergic stratum, smoking in the household was associated with a greater risk of asthma (OR 2.47; 95% CI 0.74; 7.86), although the confidence interval was wide and did not exclude no effect. In the allergic group, there was also evidence of an exposure

response relation. Compared to households with no smokers, households with 1 smoker (OR 3.42; 95% CI 0.95; 12.33) or >2 smokers (OR 5.77; 95% CI 1.59; 21) were associated with a greater risk of asthma; the latter category reached statistical significance. When total daily household cigarette consumption was examined, there was also a progressive increase in the risk of asthma: 1-19 cigarettes/day (OR 3.96; 95% CI 1.01; 15.42) and >20 cigarettes/day (OR 4.58; 95% CI 1.34; 15.68).

Peters et al., 1996. A study from Hong Kong recruited 3,521 children younger than 18 years old from two districts with good and poor air quality. As part of the study, they surveyed parents about smoking in the home and childhood asthma. ETS exposure was defined as number of different categories of exposure, defined as mother, father, siblings, lodgers, and the like. In the 1991 survey, which took place after an outdoor air pollution intervention, having two or more ETS exposure categories was associated with a greater risk of "wheezing or asthmatic symptoms" (OR 1.55; 95% CI 1.08; 2.23). The impact of ETS exposure categories on asthma alone was less strong (OR 1.22; 95% CI 0.78; 1.92). In the 1989-90 pre-intervention survey, there was no clear relation between ETS exposure and either health outcome.

Beckett et al., 1996. A population-based cross-sectional study from Connecticut recruited mothers of children less than 18 years of age. Maternal smoking was associated with a greater risk of having an asthmatic child in the family, defined as mother-reported physician-diagnosed asthma (OR 1.53; 95% CI 1.31; 1.80). In further analysis, the authors examined the impact of ETS by race-ethnicity. Among white and black families, ETS exposure was associated with a greater risk of asthma (OR 1.36; 95% CI 1.05; 1.76 and OR 1.75; 95% CI 1.12; 2.75, respectively). In the Hispanic stratum, comprised mostly of persons from Puerto Rico, there was no apparent relation between ETS exposure and asthma (OR 1.02; 95% CI 0.53; 1.96).

Stoddard and Miller, 1995. Using data from the population-based U.S. National Medical Expenditure Survey (1987), Stoddard and colleague evaluated the impact of parental smoking on current respiratory status. Asthma was defined as parent-reported "asthma or wheezing" during the past 12 months. Maternal smoking was associated with a greater risk of asthma or wheeze (OR 1.36; 95% CI 1.14; 1.62). Paternal smoking was not related to asthma / wheeze (OR 0.83; 95% CI 0.67; 1.02). The risk estimate for maternal smoking was greatest for younger children:

OR 1.90 (95% CI 1.23; 2.94) for 0-2 yrs, OR 1.53 (95% CI 0.99; 2.37) for 3-5 years; OR 1.35 (95% CI 1.01; 1.81) for 6-12 years; and OR 1.07 (95% CI 0.76; 1.49) for 13-17 years.

Table 6.31 ETS and New-onset Childhood Asthma – Case-control Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Jones *et al* 1999 U.K.	Case-control study Asthma, ctrl n=100 4-16 yr	Parental smoking Mother Father	Diagnosed asthma 1.17 (p = NS) 0.85 (p = NS)	No significant ETS association found.
Infante- Rivard *et al* 1999 Canada	Case-control study 9-11 yr n = 404	Maternal smoking >0-20 cig/d > 20 "	Persistent asthma 1.22 (0.79; 1.88) 3.84 (1.68; 8.76)	Persistent not transient asthma associated with maternal smoking
Agabiti *et al* 1999 Italy	Population-based case-control study 6-7 yr n = 18,737 13-14 yr n = 21,068	Parental smoking Any smoking Mother only Father only Both Any smoking Mother only Father only Both	Current asthma 6-7 yr 1.34 (1.11; 1.62) 1.46 (1.13; 1.87) 1.26 (1.01; 1.58) 1.35 (1.09; 1.69) 13-14 yr 1.17 (0.99; 1.39) 1.23 (0.98; 1.53) 1.04 (0.86; 1.27) 1.29 (1.06; 1.56)	Current asthma defined as history of asthma plus wheeze in last 12 mo. Any ETS increased risk in young children. Effects less pronounced in adolescents.
Yang *et al* 1998 Taiwan	Population- based case-control study. 6-12 yr n = 330	Household	Physician-diagnosed asthma 0.83 (0.54; 1.27)	Cases were parent-reported physician-diagnosed asthma; Controls had no asthma, atopy, wheeze, etc.
Ehrlich *et al* 1996 So. Africa	Case-control study Asthma n=368 Ctrls n=294 7-8 yrs	Cot/creatinine 30.6-63.5 63.6-130.1 > 130.1	Asthma or wheeze 1.21 (0.76; 1.93) 1.66 (1.04; 2.66) 1.61 (1.01; 2.58)	Asthma risk increased with cotinine and #smokers: OR 1.15 per smoker (1.01; 1.30)
Strachan & Carey 1995 UK	Case-control study Asthma n=486 Ctrls n=475	Parental smoking Mother 1-10 10 cig/d Father 1-10 > 10 cig/d	Severe asthma 1.13 (0.73; 1.74) 1.49 (0.80; 2.77) 0.97 (0.64; 1.47) 0.62 (0.32; 1.18)	No evidence of effect of paternal smoking. Maternal effect but CI includes unity.
Lindfors *et al* 1995 Sweden	Case-control study 193 Asthma 318 Ctrls 1-4 yrs	Parental smoking during 1st 2 yrs + skin test - skin test	Diagnosed asthma 2.1 (1.0; 4.2) 1.6 (1.1; 2.3)	More asthma with ETS esp. if skin test to cat or dog allergen is positive.

Table 6.31 ETS and New-onset Childhood Asthma – Case-control Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Azizi *et al* 1995 Malaysia	Case-control study Asthma n=158 Ctrls n=201 1 mo-5 yr	Parental smoking Shared bedroom with smoker	First acute asthma 1.91 (1.13; 3.21)	ETS effects but study can't distinguish induction vs exacerbation

Jones et al., 1999. Researchers recruited 100 cases of asthma from a general practice asthma register in Plymouth, U.K. These children had received a clinical diagnosis of asthma and had received asthma treatment during the past year. Each case was matched by age and gender to a control child, who had no history of asthma or respiratory symptoms. Parent-reported maternal smoking (OR 1.17) and paternal smoking at home (OR 0.85) were not associated with the risk of asthma. Confidence intervals for smoking data were not reported in this study which looked primarily at house moves, indoor air, and heating methods.

Infante-Rivard et al. (1999) published a 6 year follow-up of their initial case-control study of incident asthma cases diagnosed by a pediatrician. The original study (Infante-Rivard, 1993), which linked maternal smoking with a greater risk of incident asthma among 3-4 year-olds, was included in the 1997 OEHHA meta-analysis (Cal/EPA, 1997). Based on 6-year follow-up, the investigators classified subjects as having transient asthma (no subsequent symptoms or asthma medication use) or persistent asthma (continued symptoms or medication use). Subjects were compared to their original matched controls. Maternal smoking was associated with a greater risk of persistent asthma (OR for mean daily cigarette consumption > 0 to < 20 was 1.22; 95% CI 0.79; 1.88; for > 20 cigarettes per day OR was 3.84; 95% CI 1.68; 8.76). There was no relation between maternal smoking and transient asthma (OR 0.81; 95% CI 0.37; 1.76 for 20 cigarettes or less and OR 1.07; 95% CI 0.35; 3.26 for >20). Building on the original case-control study, this study further implicates ETS exposure as a cause of persistent asthma.

Agabiti et al., 1999. The authors conducted a case-control analysis of data from a large cross-sectional survey among Italian schoolchildren of two ages: 6-7 years (n=18,737) and 13-14 years (n=21,068). Parents completed the survey for younger children; adolescents also completed the survey. Current asthma was defined as a history of asthma plus wheezing symptoms during the past 12 months. Among children aged 6-7 years, any current parental smoking was associated with a greater risk of current asthma (OR 1.34; 95% CI 1.11; 1.62). Smoking by the mother only or the father only was also associated with a higher likelihood of current asthma (Table 6.31). Any current parental smoking was also associated with a greater risk of asthma among adolescents, although the confidence interval included no effect (OR 1.17; 95% CI 0.99; 1.39).

Yang et al., 1998. Using participants in a cross-sectional survey conducted in a subtropical region of Taiwan, investigators identified cases of parent-reported physician-diagnosed asthma and compared them to controls with no asthma history, persistent wheeze, cough, phlegm, pneumonia, or bronchitis. Household smoking by any household member was not statistically associated with asthma (OR 0.83; 95% CI 0.54; 1.27). According to the authors, many smokers in developing countries smoke lightly. Because smoking intensity was not assessed, the lack of association could be explained by low level ETS exposure.

Ehrlich et al., 1996. A population-based case-control study from South Africa recruited children who had parent-reported asthma or other respiratory symptoms such as wheezing (cases) and controls with "no or few asthma symptoms." Urine cotinine was used as a biomarker of ETS exposure. As cotinine-creatinine ratio increased, the risk of asthma progressively also increased (OR 1.21 for second vs. first quartile, OR 1.66 for third quartile, OR 1.61 for fourth quartile; Chi-square test for linear trend = 5.4 with p = 0.02). In bivariate analysis, current maternal smoking was related to a greater risk of asthma (OR 1.7; 95% CI 1.23; 2.34). Risk estimates were similar for maternal ever smoking (OR 1.8; 95% CI 1.29; 2.50) and maternal smoking during the child's first year of life (OR 1.7; 95% CI 1.20; 2.35). There also appeared to be exposure-response relationships for daily maternal cigarette consumption and number of household smokers. In multivariate analysis that included maternal smoking during pregnancy, current maternal smoking was less strongly associated with asthma (OR 1.33; 95% CI 0.85; 2.00). Number of household smokers was related to a greater risk of asthma (OR 1.15 per smoker; 95% CI 1.01; 1.30).

Strachan and Carey, 1995. A population-based case-control study from Sheffield, England identified 486 cases of severe asthma based on parental reports of >12 wheezing attacks or >1 speech-limiting attack of asthma during the past year. Controls (n = 475) with no history of asthma or wheezing were matched on age and school class. Low-level maternal smoking (1-10 cigarettes/day) was not related to the risk of severe asthma (OR 1.13; 95% CI 0.73; 1.74). Higher level maternal smoking (>10 cigarettes / day) was associated with a greater risk of severe asthma, but the confidence interval was wide and did not exclude no impact (OR 1.49; 95% CI 0.80; 2.77). Paternal smoking was not associated with the risk of severe asthma.

Lindfors et al., 1995. This case-control study from Sweden recruited cases of childhood asthma (age 1-4 years) from an allergy clinic. Because inclusion criteria required three or more episodes of asthma exacerbation, cases had moderate-to-severe asthma (most had recent hospitalization or emergency department visits for asthma). A random sample of controls were selected from the same catchment area, matched on age. The analysis was stratified by whether or not children had a positive skin test to dog or cat allergen. Among the skin test positive subjects, parent-reported smoking during the child's first two years of life was associated with a greater risk of asthma (OR 2.1; 95% CI 1.0; 4.2). A similar relation was observed in the skin test negative stratum (OR 1.6; 95% CI 1.1; 2.3).

Azizi et al., 1995. A study from Kuala Lumpur, Malaysia recruited 158 cases, defined as children with their first hospitalization for acute asthma, and 201 controls, who were hospitalized for non-respiratory causes. Controls were matched on age and day of admission. Sharing a bedroom with a smoker was associated with a greater risk of asthma hospitalization (OR 1.91; 95% CI 1.13; 3.21). One difficulty in interpreting this study is that the case definition could capture children with new-onset asthma or exacerbation of pre-existing asthma. As a consequence, the separate effects of ETS on asthma induction and exacerbation cannot be clearly separated.

Table 6.32 ETS and New-onset Childhood Asthma - Cohort Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Jaakkola *et al* 2001 Norway	Cohort study: 0-4yr n = 2,531	Parental smoking Smoke at birth	Bronchial obstruction OR 1.43 (1.07; 1.90) asthma 1.10 (0.79;1.53)	More ETS effect on bronchial obstruction by age 2 than on asthma
Ponsonby *et al* 2000 Australia	Cohort study: 0-7 yrs n=863	Smoker in same room	Current asthma at 7 yr 1.52 (1.01; 2.29)	Exposure-response suggested: 1.04/20 cig (0.99; 1.10)
Tariq *et al* 2000, 1998 U.K.	Cohort study: 0-4 yrs n=1218	Maternal report at 1 yr of age 2 yr 4 yr	Asthma prevalence 2.5 (1.7; 3.7) 2.2 (1.5; 3.4) 1.2 (0.3; 2.7)	ETS increased asthma but focus was on prevalence not incidence
Oddy *et al* 1999 Australia	Birth cohort study Followed to age 6 n = 2,187	Home ≥ 1 cig/day	Asthma 1.27 (1.04; 1.55)	Physician-diagnosed asthma elevated after control for sex, age, breastfeeding, and childcare attendance.
Wennergren *et al* 1997 Sweden	Cohort study: dx 2 yr follow-up 10 yr n = 92	Parental smoking ETS infancy ETS age 10	Asthma persistence vs not at 10 yr 82 vs 59% p=0.05 54 vs 52% p=NS	Exposure during infancy more critical than later.

Jaakkola et al., 2001. The Oslo birth cohort study followed children from birth through age 4 years. Of the 3,754 children enrolled at birth, 2,985 completed two-year follow-up and 2,531 were traced at 4 years. ETS exposure was defined as parent-reported smoking at the time of the child's birth. Two related health outcomes were examined: asthma at age 4 years, which was defined as parent reported physician-diagnosed asthma plus respiratory symptoms during the previous 12 months; and bronchial obstruction during the first two years of life, which was defined as two or more episodes of respiratory symptoms or one episode lasting more than one month. ETS exposure was associated with a greater risk of bronchial obstruction during the first two years of life (OR 1.43; 95% CI 1.07 - 1.90). The relation between ETS exposure and asthma was less clear (OR 1.10; 95% CI 0.79 - 1.53).

The investigators further examined the joint effects of genetic predisposition to asthma, defined as parental asthma or hay fever, and ETS exposure. For both bronchial obstruction and asthma, the risks conferred by ETS and genetic predisposition were more than additive (i.e., synergistic). The risk of asthma associated with both genetic predisposition and ETS exposure (OR 2.68; 95% CI 1.70; 4.22) was greater than that for genetic predisposition or ETS exposure alone (OR 1.66; 95% CI 1.08; 2.54 and OR 0.84; 95% CI 0.53; 1.34).

Ponsonby et al., 2000. A cohort study from Australia evaluated 863 children at age 7 years who had previously participated in an infant cohort study. The investigators examined the relation between parent-reported ETS exposure during infancy and current asthma at age 7 years. The analysis was stratified according to whether household residents smoked ("smoker households") or did not smoke ("non-smoker households"). Compared to smoker households where no one ever smoked in the same room as the baby, infants whose mothers or others smoked in the same room as the baby had an increased risk of current asthma at age 7 years (RR 1.52; 95% CI 1.01; 2.29). In non-smoker households, there was no relationship between any smoking in the baby's room and subsequent asthma (RR 0.65; 95% CI 0.38; 1.13). There was a suggestion of an exposure-response response relationship between number of cigarettes smoked in the home during infancy (reported during the past 48 hours) and the risk of asthma at age 7 years (RR 1.04 per 20 cigarettes; 95% CI 0.99; 1.10).

Tariq et al., 2000; Tariq et al., 1998. Investigators from the Isle of Wight (U.K.) followed a population-based birth cohort of 1,218 infants through age 4 years. Asthma was diagnosed based on clinical criteria. Parental smoking was updated at each age. Maternal smoking was associated with a greater risk of asthma at age 1 year (OR 2.5; 95% CI 1.7; 3.7) and 2 years (OR 2.2; 95% CI 1.5; 3.4). There was no statistical relationship at age 4 years (OR 1.2; 95% CI 0.3; 2.7). Study limitations include a focus on asthma prevalence at each age, rather than on asthma incidence. In addition, no longitudinal analysis of postnatal ETS exposure on subsequent asthma risk was conducted.

Oddy et al., 1999. A birth cohort study of 2,187 children living in Western Australia evaluated the impact of breastfeeding on parent-reported physician-diagnosed asthma. In this study, smoking in the household, as defined by one or more cigarettes smoked inside the house per day, was associated with a greater risk of asthma (OR 1.27; 95% CI 1.04; 1.55), controlling for sex, gestational age, breastfeeding, and childcare attendance.

Wennergren et al., 1997. A cohort study re-investigated children at 10 years of age who had been previously hospitalized for acute asthma before age 2 years. After 10 years, only 30% of children had symptomatic, persistent asthma. At 10-year follow-up, the proportion of children with persistent asthma who had previous ETS exposure during infancy was higher than that of symptom-free children (82% vs. 59%, p=0.05). At age 10 years, the proportion of children with current ETS exposure was similar among those with persistent asthma vs. no asthma (54% vs. 52%). These results suggest that early childhood ETS exposure had more influence on the risk of persistent asthma than continued exposure later in childhood. Alternatively, parents with symptomatic children may be more likely to quit smoking.

6.3.2.1. Asthma in Childhood: Meta-analyses and Conclusions

Based on considerable epidemiological evidence, the 1997 Cal/EPA report concluded that there is compelling evidence that ETS exposure causes new-onset childhood asthma. Supporting this conclusion, OEHHA conducted a meta-analysis of 37 studies that evaluated the impact of ETS exposure on childhood asthma induction. The 1997 OEHHA report elaborated as follows.

> "There appears to be a simple biological gradient of effect (or dose-response) in studies that collected data on levels of smoking, where effects were detectable only when the

> mother smoked 10 or more cigarettes per day (*e.g.*, Martinez *et al.* 1992). This finding suggests that a threshold of ETS exposure intensity is required in order to evoke this response. The temporal relation between childhood asthma and parental smoking is not at issue here, since asthma in children is unlikely to precede active smoking by their parents. However, it might be argued that, since the association seems to be strongest between maternal smoking and asthma prevalence in pre-school children, the key exposures may have taken place *in utero*. Several recent studies suggest that pre-natal exposures may cause persistent decrements in lung growth and development (Cunningham *et al.* 1994, 1995, Hanrahan *et al.* 1992). It is possible that pre-natal effects may play a role as well in the etiology of childhood asthma. However, the studies by Chen (1986, 1988, 1989), showing effects of paternal smoking alone, as well as studies of ETS exposure linked to increased risks of asthma in nonsmoking adults (Leuenberger *et al.,* 1994), indicate that post-natal exposures can be sufficient to elicit this outcome. Development of asthma as a result of ETS exposure is "coherent" with other investigations demonstrating that both active and passive exposure to cigarette smoke are associated with increases in airway responsiveness, which (as noted above) is a characteristic feature of asthma. The biological plausibility of this relationship is strong: (1) ETS exposure predisposes young children to an increased risk of repeated respiratory infection, a recognized risk factor for the development of asthma; (2) ETS causes airway hyperresponsiveness; (3) ETS may increase the risk of childhood atopy and of increased circulating allergy-related antibodies (IgE), enhancing the probability of allergic asthma; (4) cigarette smoke causes airway inflammation in active smokers (Niewoehner, 1974) and may have similar (but lower-level) effects in people exposed to sidestream smoke. Taken as a whole, the epidemiologic evidence of causation is compelling."

OEHHA conducted an update of the meta-analysis found in the 1997 document to examine the association between exposure to ETS in the home and the development of childhood asthma. OEHHA surveyed 85 studies, covering over 460,000 children, and representing 29 countries. For the purposes of meta-analysis, relative risk estimates were extracted according to preset exclusion/inclusion criteria, and represented various combinations of exposure and outcome definition, subgroup stratification, and levels of exposure. To make ORs more comparable between studies, exposure levels for measures of cigarettes smoked per day, number of

household smokers and cotinine levels were normalized. A correction formula was applied to convert ORs to RRs among cross-sectional and cohort studies with greater than 10% asthma prevalence. The degree of inter-study heterogeneity and a pooled estimate of risk were derived from a random-effects model after evaluation of the data by both fixed- and random effects models.

Analyses based on 29 studies that controlled for the child's history of atopy and personal smoking, and in which all ages were combined gave a pooled OR for new-onset asthma of 1.32 (95% CI, 1.24; 1.41). The test for heterogeneity gave Q = 30.63 (p = 0.334) and a between-study variance of 0.002. A subset of these studies, comprising 5 birth cohort studies, was used to examine the effects of exposure duration. Based on this analysis, the risk (RR) of asthma onset among children exposed to postnatal ETS for 5 years was 1.22 (95% CI 1.16; 1.34), and 1.42 (95% CI 1.28; 1.70) following 10 years of exposure. Of the 29 studies, 23 controlled for age and gender with an RR of 1.29 (95% CI 1.21; 1.37). Additional control for race raised the RR to 1.35 (95% CI 1.21; 1.50).

While preschool children appeared to be more at risk than older children (RR 1.44, 95% CI 1.04; 1.99 vs RR 1.26, 95% CI 1.19; 1.32), it is notable that the risk for asthma onset was not limited to young children or those exposed during pregnancy. Older children exposed to ETS were also at significant risk for new onset asthma (see Table 6.33).

Table 6.33 Subgroup Analysis of Asthma Induction Risk after ETS Exposure

Study characteristic	N*	Pooled RR	95% CI
Case-control (CC)	7	1.36	1.15; 1.61
Cross-sectional (XS)	14	1.28	1.18; 1.39
Cohort (incident cases)	8	1.27	1.14; 1.42
CC & XS prevalent cases	21	1.33	1.23; 1.43
Hospital/clinic case source	7	1.45	1.14; 1.85
Community case source	22	1.27	1.20; 1.35
Included older children	24	1.26	1.19; 1.32
Restricted to preschool	5	1.44	1.04; 1.99
Control by age and sex	23	1.29	1.21; 1.37
No control by age and sex	6	1.35	1.07; 1.70
Control by race	17	1.35	1.21; 1.50
No control by race	12	1.24	1.17; 1.32

*N = number of studies included in pooled estimate

From subset analysis it was noted that estimates based on studies that identified asthma cases from hospital and clinical records were higher than those based on community- based surveys or interviews (RR 1.45, 95% CI 1.13; 1.84 and 1.27, 95% CI 1.20; 1.35, respectively). Disease misclassification in community surveys may have contributed to lower risk estimates in some of the earlier studies (see Table 6.33).

The timing of ETS exposure (pre- vs postnatal) was examined in the studies listed in Table 6.34. Six of the studies that combined pre- and postnatal exposures had elevated ORs, four of them significantly so. In the studies reporting postnatal compared to combined pre- and postnatal exposures, the risks were generally higher for the combined exposure. Postnatal-only exposure resulted in elevated asthma risk in seven of eight studies, and that risk was statistically significant in three of the studies.

Table 6.34 Effect of Timing of ETS Exposure on Risk of Asthma Induction

Study author	Age range	Exposure timing*	RR	95% CI
Azizi *et al.*, 1995[h]	1 mo-5.5 yr	Postnatal only	1.91	1.13; 3.21
Mannino *et al.*, 2001[h]	4 – 6 yr	Pre-& postnatal	4.31	2.15; 6.58
"	"	Postnatal only	3.20	1.34; 5.68
Agabiti *et al.*, 1999[m]	6 – 7 yr	Pre-& postnatal	1.62	1.34; 1.96
"	"	Postnatal only	1.12	0.93; 1.35
Neuspiel *et al.*, 1989[m]	0 – 10 yr	Pre-& postnatal	1.56	1.30; 1.87
"	"	Postnatal only	2.3	1.26; 4.22
Hajnal *et al.*, 1999[m]	6 – 14 yr	Pre-& postnatal	1.31	0.92; 1.85
Mannino *et al.*, 2001[h]	7 – 11 yr	Pre-& postnatal	0.63	0.22; 1.58
"	"	Postnatal only	0.91	0.43; 2.15
Azizi & Henry, 1991[h]	7 – 12 yr	Postnatal only	1.08	0.91; 1.61
Gilliland *et al.*, 2001[h]	9 – 15 yr	Pre-& postnatal**	1.24	0.91; 1.61
"	"	Postnatal only	1.24	0.91; 1.54
Agabiti *et al.*, 1999[m]	13 - 14	Pre-& postnatal	1.22	1.02; 1.47
"	"	Postnatal only	1.15	0.99; 1.34

[h] household exposure; [m] maternal exposure; *exposure status based on current smoking; **exposure status based on ever-smoking.

From the pooled estimate, we concluded that the risk of developing asthma was likely in the range of 1.21 to 1.37. We also concluded that the meta-analysis suggested an assessment of causality and that the relationship between ETS exposure and asthma induction is causal.

Several features of this study strengthen the evidence suggesting a causal association between ETS exposure and asthma in children. The analysis emphasized studies of recognized or diagnosed asthma rather than those that included wheeze alone, thereby limiting disease misclassification. In the studies selected for analysis, cases and controls were selected by the same criteria. To facilitate comparison, exposure level values were normalized from the entire range of smoking levels in the study population rather than a subset of exposure levels. Pooled studies all controlled for confounding by the child's own smoking history and history of atopy. We also included an analysis for publication bias by the Begg and Mazumdar (1994) rank sum correlation procedure. No evidence of publication bias was found ($z = 1.58$, $p = 0.115$). It thus appears unlikely that unmodeled confounding and publication bias can explain the association between ETS and asthma reported in this study. Based on the risk estimate range given above, an asthma prevalence of 9.4% and ETS exposure prevalence of 11.4% among the 9,250,000 children 0-17 years old, it is possible to calculate an attributable risk. Using a non-threshold model (Lilienfeld and Lilienfeld, 1980), the authors estimate that the number of prevalent cases of asthma among children 0-17 years of age in California in 2001 that are attributable to ETS exposure is 31,000 (24,000-40,000).

The current review of 37 recent studies and OEHHA's more recent meta-analysis of 85 studies strongly support the original conclusion in the OEHHA 1997 document that ETS exposure is causally associated with new-onset asthma among children

6.3.2.2. Attributable Risk Calculation

As the OEHHA analysis continues to support a causal association of asthma onset and exacerbation and ETS exposure it is thus possible to estimate the number of cases of childhood asthma attributable to ETS exposure.

State and national surveys quantifying asthma in children generally include persons reporting being diagnosed with asthma by a physician at any time and reporting symptoms of asthma during the preceding 12 months. According to CDC's asthma surveillance report, in 1999 among children ≤14 yrs of age, the number of children with attacks or episodes was 3,113,000 (CDC, 2002). This estimate is limited to children ≤14 years of age and thus does not include

cases among individuals 15-17 years of age. As reported in the meta-analysis by Vork *et al*., the risk of developing childhood asthma after exposure to ETS is 1.32.

For California, an exposure level of 11.4% represents the percentage of children 0-17 yrs old in households not protected from ETS (CDHS, 2001). This exposure level may be low as it does not include exposures occurring outside the home that become relatively more important among older children. An attributable fraction may be calculated:

a = 0.035 [0.114(1.32-1)/(0.114(1.32-1)+1].

The California Health Interview Survey reported an asthma symptom prevalence of 9.6% among children 0-17 years old in 2000 (CHIS, 2001). In 2000 there were 9,257,588 children 0-17 years of age. Active smoking prevalence was 1.8% among 12-13 year olds, 5.5% among 14-15 year olds and 16.2% among 16-17 year old children. This left 9,026,316 nonsmokers 0-17 years of age of whom 867,000 had asthma. Using the attributable fraction above of 0.035, the number of individuals with at least one ETS-attributable asthma episode in the previous 12 months was approximately 31,000. Since this represents the number of individuals affected but not the number of individual asthma episodes, this may significantly underestimate the actual number of ETS-related asthma events.

Similarly for the US, with an exposure rate of 21.9% (CDC, 1997), there were 202,300 individuals 0-14 years of age with ETS-related asthma episodes [0.219(1.32-1)/(0.219(1.32-1)+1) = 0.065; 0.065 x 3,113,000 = 202,300.

6.4. Acute Health Effects (Adults)

6.4.1. Asthma (exacerbation)

6.4.1.1. Previous Findings on Asthma Exacerbation in Adults

Because adults with asthma have chronic airway inflammation, they may be particularly susceptible to the effects of ETS exposure. As reviewed above, ETS exposure has been strongly linked with exacerbation of pre-existing asthma among children. Adults with asthma commonly report ETS exposure as a trigger for asthma exacerbation (Abramson *et al.*, 1995; Dales *et al.*, 1992). However, the impact of ETS exposure on adults with asthma has received less research than in children.

Based on the review of studies focusing on children or adults, the previous Cal/EPA report concluded that the evidence "…supports the existence of an association of chronic or repeated ETS exposure with severity of asthma measured by a variety of indices." Because most of these studies evaluated children, the Cal/EPA report tempered its conclusions about adults: "…there is suggestive evidence that ETS exposure may exacerbate adult asthma."

6.4.1.2. New Epidemiological Findings in Adults

More recent studies, shown in Table 6.40 and described below, substantiate the assertion of evidence that ETS exposure may exacerbate adult asthma.

Table 6.40 ETS and Adult Asthma Exacerbation

Reference Country	Study description	ETS exposure measure	Findings and OR (95% CI)	Comments
Eisner *et al.* 2002 US	Cross-sectional: Cotinine and pulmonary function asthmatics n = 440	NHANES Serum cot in nonsmoking asthmatics	FEV_1 in women -261 ml (-492 to -30) FVC, FEV_1/FVC also impaired	Elevated serum cotinine associated with pulmonary function deficits in women but not men. Asthmatics more affected than general pop.
Eisner *et al.* 2001 US	Prospective cohort 7 day; respiratory symptoms in adult asthmatics 18-50 yr n = 50	Nicotine badge 0-0.05 µg/m^3 > 0.05 " 0-0.05 µg/m^3 > 0.05 "	Resp. symptoms OR 1.9 (0.4; 8.8) 6.8 (1.4; 32.3) Bronchodilator use OR 2.2 (0.3; 15) 8.1 (1.3; 50)	Nicotine measured by personal badge associated with increased bronchodilator usage and respiratory symptoms. Linear exposure-response.
Tarlo *et al.* 2000 Canada	Nested case-control Exacerbation of asthma 13-55 yr.* n = 42	ETS past year Exacerbation Controls	Reported ETS exposure 39% 17% p<0.03	More cases (adults and adolescents) with exacerbation of asthma reported ETS exposure in previous 12 mo.
Kunzli *et al.* 2000 Switzerland	Cross-sectional: pulmonary function in asthmatic adults 18-60 yr n = 3534	Self report FEV_1 FVC $FEF_{25-75\%}$	% change -4.8 (-9.2; 0) -1.7 (-5.5; 2.1) -12.4 (-20.4; -3.7)	ETS at work decreased pulmonary function in women more than men. Linear exposure-response trend for hrs per day and # years exposed.
Jindal *et al.* 1999 India	Cross-sectional: pulmonary function women w/asthma 20-40 yrs n = 50	Home, work questionnaire	ETS vs none PD_{20} 1.7 vs 6.1 p<0.01 No difference in FEV_1, FEV/FVC	ETS increased bronchial hyperresponsiveness (↓PD_{20}). ETS increased continuous bronchodilator use (39% vs 26%; p<0.05)
Sippel *et al.* 1999 US	Prospective cohort health outcomes in asthmatics 15-55 n = 619	Self report ETS No ETS Hospital care	Asthma care events 28/100 person-yrs 10/100 " OR 2.34 (1.8; 3.1)	ETS associated with worse health status and asthma-specific quality of life at baseline, and more hospital-based care during follow-up.
Eisner et al 1998 US	Case-crossover Bartenders Resp. health n = 53	Self report and spirometry before/after smoking ban	Respiratory symptoms per 5-hr reduction in ETS 0.7 (0.5; 0.9)	74% reported symptoms before ban, 32% after ban. FVC and FEV1 improved after ban.

FEF_{25-27} forced expiratory flow at 25-75% of vital capacity; FEV_1 forced expiratory volume in one second; FVC forced vital capacity; PD_{20} histamine dose to give 20%decrease in FEV_1. *This study included adolescents with adults.

Eisner, 2002. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), Eisner examined the relationship between serum cotinine and pulmonary function among 440 non-smoking adults with asthma (corresponding to a population of 4.9

million asthmatics). There was no apparent impact of ETS exposure, as measured by serum cotinine level, on pulmonary function among men. In the female stratum, higher levels of ETS exposure were associated with greater impairment of FEV_1, FVC, and FEV_1/FVC ratio. In particular, the highest cotinine tertile was related to a mean FEV_1 decrement of -261 ml (95% CI -492; -30). The impact of ETS exposure appeared to be greater among adults with asthma compared to non-smoking members of the general population.

Eisner et al., 2001. To study the impact of ETS exposure on adults with asthma, Eisner and colleagues used data from an ongoing prospective cohort study of adults with asthma recruited from a random sample of allergy, pulmonary, and family practice physicians practicing in Northern California. Of the overall cohort, 50 subjects were recruited to wear a personal nicotine badge monitor for one week. At the conclusion of the monitoring period, respiratory symptoms and medication use were ascertained. Compared to subjects with no measurable nicotine levels for the past 7 days, lower level (0-0.05 $\mu g/m^3$) and higher level exposures (>0.05 $\mu g/m^3$) were associated with a greater risk of respiratory symptoms at follow-up (OR 1.9; 95% CI 0.4; 8.8 and OR 6.8; 95% CI 1.4; 32.3). Lower- and higher-level ETS exposures were also related to an increased risk of extra bronchodilator use after exposure (OR 2.2 and 8.1). For both outcomes, there was evidence of a linear exposure-response relationship (p value for trend 0.017 and 0.022 respectively).

Tarlo et al., 2000. A prospective cohort study from Canada followed children and adults with asthma for the development of acute exacerbation. The main goal was to evaluate the impact of viral upper respiratory infections on the risk of asthma exacerbation. In this study, subjects less than 13 years of age were considered children, while adolescents were included with adults. More than half of subjects were aged 13 years or older (58%), ranging up to age 55 years. Within the cohort, a nested case-control study was performed, with cases of acute asthma exacerbation compared to controls without exacerbation. Cases with asthma exacerbation were defined by increasing asthma symptoms refractory to usual medications for more than 48 hours or urgent health care utilization for asthma: hospitalization, emergency department visit, or urgent physician visit. Cases (with acute asthma exacerbation) were more likely to have indicated ETS exposure during the previous year (39%) than controls without exacerbation (17%) ($p<0.03$). Although the investigators ascertained exposures to colds, dust, and other

factors during the week preceding the exacerbation, ETS exposure was not reported for this period.

Kunzli et al., 2000. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) focused on a random sample of adult never-smokers aged 18-60 years residing in Switzerland. A report from the SAPALDIA investigators found similar effects of self-reported ETS exposure on pulmonary function among 3534 never smoking adults with asthma. ETS exposure at work was related to an average decrement of FEV_1 (-4.8%, 95% CI –9.2; 0), FVC (-1.7%, 95% CI –5.5; 2.1), and forced expiratory flows at mid-lung volumes ($FEF_{25\%-75\%}$ -12.4%, 95% CI –20.4; -3.7). The impact of ETS exposure on FEV_1 and $FEF_{25\%-75\%}$ was greater among women than men (-8.7% vs. 0.5% and -20.8% vs. -1.4%, respectively). There was evidence of linear exposure-response trend for daily exposure duration and years of exposure.

Jindal et al., 1999. In a cross-sectional study, Jindal and colleagues recruited 50 women with asthma from a university hospital chest clinic in India. ETS exposure at home and work was assessed by questionnaire. Compared with women who indicated no ETS exposure, subjects indicating any ETS exposure had similar FEV_1 (78% predicted vs.79%) and FEV_1/FVC ratio (94% vs. 86%) (p = N.S. in both cases). The ETS-exposed women had greater bronchial hyperresponsiveness, as indicated by lower PD_{20}, the amount of histamine required to produce a 20% decrease in FEV_1 (median 1.70 vs. 6.1 units; $p<0.01$). ETS exposure was also associated with greater asthma medication use. The proportion that indicated "continuous" bronchodilator use was higher among exposed women (39% vs. 26%; $p<0.05$), although the precise definition of this term was not provided. Taken together with the European Community Respiratory Health Survey, ETS exposure is related to greater bronchial hyperresponsiveness among adults with asthma.

Sippel et al., 1999. A cohort study of 619 adult HMO members with asthma evaluated the association between ETS exposure and health outcomes. The prevalence of self-reported regular ETS exposure was 38% and a small proportion of subjects (11%) indicated current personal cigarette smoking. In cross-sectional analysis of baseline data, regular ETS exposure was associated with worse asthma-specific quality of life (QOL) and generic health status (physical functioning and general health domains). During longitudinal follow-up, ETS exposure was

associated with a greater incidence of hospital-based episodes of asthma care (28 events vs. 10 events per 100 person-years). After controlling for socio-demographic covariates, ETS exposure was associated with a greater risk of hospital-based care (RR 2.34; 95% CI 1.8; 3.1).

Eisner et al., 1998. Using a case-crossover design, the effects of California State Assembly Bill 13, which prohibited tobacco smoking in bars and taverns, on the respiratory health of bartenders was studied. Based on a random sample of all bars and taverns in San Francisco, the authors interviewed and performed spirometry on 53 bartenders before and after the smoking ban. After prohibition of smoking, self-reported workplace ETS exposure sharply declined from a median of 28 to 2 hours per week. Thirtynine (74%) of the 53 bartenders reported at least one respiratory symptom at baseline (including cough, dyspnea, and wheezing), while only 17 (32%) were still symptomatic at follow-up. Of the 39 bartenders reporting baseline symptoms, 23 subjects (59%) no longer indicated any respiratory symptoms after prohibition of smoking ($p<0.001$). In particular, 70% of the 17 bartenders reporting baseline wheezing noted resolution after workplace smoking prohibition. In conditional logistic regression analysis, a 5-hour reduction of workplace ETS exposure was associated with a lower risk of respiratory symptoms at follow-up (OR 0.7; 95% CI 0.5; 0.9), after controlling for upper respiratory infections and reduced personal cigarette smoking. After prohibition of workplace smoking, improvement in mean FVC (0.189 L; 95% CI 0.082; 0.296) and mean FEV_1 (0.039; 95% CI -0.030; 0.107) was observed. Complete cessation of workplace ETS exposure was associated with an even greater pulmonary function improvement.

6.4.1.3. Controlled Human Exposure Studies (adults)

The 1997 Cal/EPA report reviewed 10 controlled human exposure studies that focused on persons with asthma. Most of the studies indicated slight-to-moderate transient effects on pulmonary function. The report concluded that the "…controlled exposure studies do not clearly demonstrate a consistent effect of acute ETS exposure on asthmatics as a whole." There have been few subsequent controlled human exposure studies among adults with asthma.

Nowak et al., 1997a. In 17 adult subjects with mild asthma, experimental ETS exposure for 3 hours resulted in greater reduction in mean FEV_1 (5.6%) compared to a sham exposure group (3.0%) ($p=0.013$). As measured by methacholine challenge, there was a tendency toward greater

responsiveness in the ETS exposure group, but the results were not statistically significant (p=0.18). Another study by the same investigators exposed 10 adults with mild asthma to ETS in an experimental chamber. Compared to the sham group, there was no "significant" difference in the change of FEV_1 (0.8% decrease vs. 1.4% increase).

Interpretation of controlled exposure studies is limited by small sample size, substantial inter-individual heterogeneity in response to ETS, and variable chamber exposure methodology. The recent evidence from chamber studies is consistent with the 1997 OEHHA report's conclusion that there may be a small effect of experimental ETS exposure on pulmonary function, but these findings have not been consistent. In addition, the response of people with mild asthma may be under-predictive of the response of those with moderate to severe asthma. For medical and ethical reasons controlled exposure studies are not performed in those with more severe disease.

6.4.1.4. Summary of Acute Effects in Adults

Examination of the Bradford Hill (1971) criteria supports a causal association between ETS exposure and exacerbation of adult asthma. Several studies demonstrated an exposure-response relationship between ETS exposure and exacerbation of adult asthma {Eisner *et al*., 2001; Kunzli *et al*., 2000; Eisner, 2002} The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies, especially the longitudinal cohort studies. Biologic plausibility is supported by the fact that ETS includes potent respiratory irritants and immunotoxicants; and exposure has been linked to greater bronchial hyperresponsiveness.(Janson *et al*. 2001; Jindal *et al.,* 1999). The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, ETS has been consistently linked with poorer asthma status. The relationship between ETS exposure and asthma has also been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. The studies reviewed also demonstrate coherence in the association between ETS exposure and exacerbation of adult asthma. ETS exposure has been associated with an adverse impact on a variety of asthma outcomes, including diverse endpoints such as respiratory symptoms, pulmonary function, and hospitalization for asthma. Taken together, the evidence is consistent with a causal effect of ETS on adult asthma exacerbation.

6.4.2. Sensory Irritation and Annoyance

In the 1997 Cal/EPA report, OEHHA staff reviewed data on "… acute and reversible irritative effects of ETS on the upper respiratory tract… [including] eye, throat, and nasal irritation, rhinorrhea, nasal congestion, hoarseness, and odor 'annoyance'." Reference was made to previous reviews of the subject in both the Surgeon General's and NRC reports (U.S. DHHS, 1986; NRC, 1986, as well as by Samet *et al.*, 1991). The 1997 Cal/EPA report concluded that "ETS exposure produces a variety of irritative symptoms involving the upper respiratory tract... In addition to irritation, odor annoyance may detract significantly from subjective well-being and productivity among building occupants."

The above conclusion was based upon review of both controlled human exposure (chamber) and field (epidemiological) studies of ETS exposure and upper airway/mucous membrane symptoms. Since the publication of the 1997 Cal/EPA report, additional chamber and epidemiological studies have been completed. Some of the epidemiological studies have a longitudinal component, with questionnaires and/or objective testing being administered to the same subjects before and after a smoking prohibition affecting potential ETS exposure. In this context, these studies assume the status of "natural experiments." In addition to chamber and field studies, OEHHA staff identified two “miscellaneous” health studies: one animal experiment involving ETS exposure and eye irritation, and one retrospective study of ETS exposure and the risk of laryngospasm among pediatric patients undergoing general anesthesia. Finally, an industrial hygiene survey of California buildings with designated smoking areas is reviewed. These studies are summarized below, organized by study type.

6.4.2.1. Definitions (from Cal/EPA, 1997)

> "… '*Sensory irritation*' refers to subjectively reported tingling, stinging, burning, or pain involving the mucous membranes of the upper respiratory tract and/or cornea (in humans), or to [unconditioned] aversive responses to an airborne chemical agent in experimental animals. When associated reflex physiologic alterations are present (e.g., changes in airway caliber, respiratory behavior, or blink rate), they are so indicated. '*Pathological irritation*' refers to irritant-related changes in tissue structure and/or biochemical function, including necrosis, mucosal desquamation, vascular congestion, cellular infiltration, and/or release of inflammatory mediators.

6.4.2.2. Epidemiological Studies

Table 6.41 Occupational Exposure to ETS

Reference Country	Study Description	Exposure to smoke	Findings and OR (95% CI)	Comments
Mizoue *et al.* 2001 Japan	Cross-sectional study of ETS and non-specific building-related illness in 1,281 municipal workers	ETS hrs/day ≥ 4 vs < 1	Adj OR Symptoms 2.7 (1.6; 4.8) Eye, nose, throat, skin symptoms increased with increasing exposure.	Symptoms persisted after adjustment for age, gender, stress, video use, and lifestyle
Jones *et al.* 2001 New Zealand	Surveyed restaurant workers about ETS- related symptoms. 435 interviews	ETS at work	59% exposed at work with >50% reporting throat or lung irritation.	75% of interviewees favored smoking restriction in bars.
Wieslander *et al.* 2000 Sweden	Survey of 80 airline crew on 40 smoking, 40 nonsmoking flights for respiratory symptoms, cabin air quality (CAQ)	In flight: Smoking Nonsmoking	Respirable particulates: 66 $\mu g/m^3$ 3 $\mu g/m^3$	On nonsmoking flights, CAQ improved, fewer respiratory symptoms Improved mucous membranes and tear film stability.
Eisner *et al.* 1998 US	Survey of bartenders' respiratory symptoms before and after ban of workplace smoking n = 53	Pre-ban ETS: 28 hr/wk. Post-ban: 2 hr/wk.	Sensory irritation (eye, nose, throat), reported by 41 bartenders, resolved for 32 (78%) after smoking ban ($p<0.001$).	Smoking ban associated with rapidly improved respiratory health as measured by FVC and FEV_1.
Raynal *et al.* 1995 US	Assessed respiratory symptoms in 375 workers that improved outside of work in smoke-permitted office. 22 Ctrls	ETS in office with open-plan smoking policy	Among nonsmokers, positive association between area nicotine and reported symptoms esp. eye, nose and throat irritation ($r=0.165$; $p<0.01$)	Non-smokers validated by salivary cotinine. Active smokers had fewer symptoms than nonsmokers for given area nicotine levels.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity

Mizoue et al. (2001) examined data from a 1998 cross-sectional survey of 1,281 municipal employees who worked in a variety of buildings in a Japanese city. The authors were interested in overtime work and ETS exposure as determinants of symptoms consistent with non-specific building-related illness or "sick building syndrome" (SBS). Potential confounders, which were

adjusted for in a logistic regression model, included age, gender, hierarchical position, use of video display terminal > 4 hours/day, psychological stress at work, and lifestyle factors. Using workers exposed to ETS for less than one hour/day as the reference group, the odds ratio for the SBS symptom constellation among nonsmokers exposed to ETS $\geq$ 4 hours/day was 2.7 (95% CI: 1.6, 4.8). For symptoms referable to the eyes, nose, throat, and skin, odds ratios increased with increasing hours of ETS exposure. These relationships persisted after adjustment for all covariates, including overtime, which was an independent predictor of SBS symptoms.

Jones et al. (2001) surveyed bar staff, waiters, and restaurant managers and owners in New Zealand to determine attitudes and beliefs regarding the health consequences of ETS exposure. A minor component of the questionnaire also dealt with ETS-related symptoms and annoyance. The investigators were able to complete 435 interviews at 364 of an originally targeted 472 locations. The self-reported ETS exposure prevalence among respondents was 59%. More than half of those exposed to ETS reported irritation from second hand smoke to their "throat or lungs," and three-quarters of interviewees indicated that they wanted some sort of smoking restriction in bars.

Wieslander et al. (2000) surveyed 80 commercial aircraft crew members on smoking-permitted and smoking-prohibited international flights of long (11-12 hour) duration. Interviews and physical examinations were conducted, including 39 performed in-flight and 41 post-flight. Half of the flights permitted smoking, and the other half occurred soon after a smoking ban. Endpoints included cabin air quality (CAQ - both measured and perceived), upper respiratory tract/mucous membrane symptoms, tear-film stability, nasal patency (by acoustic rhinometry), and biomarkers in nasal lavage fluid (eosinophilic cationic protein, myeloperoxidase, lysozyme, and albumin). Cabin air was found to be of low relative air humidity (2-10%) although carbon dioxide concentrations - a surrogate for the adequacy of ventilation relative to occupancy - were in an acceptable range. Total respirable particles were reduced dramatically by the smoking ban, with the mean falling from 66 to 3 $\mu g/m^3$. The perceived CAQ was improved, and symptoms - particularly ocular - were less prevalent on non-smoking flights. In terms of objective endpoints, tear-film stability increased after the smoking ban, and although there was a trend toward increased nasal patency, it was not consistent by study subgroup. The authors concluded that in-

flight ETS exposure is associated with poor perceived air quality, as well as with symptomatic and [selected] objective indices of upper respiratory tract/mucous membrane irritation.

Eisner et al. (1998) obtained a random sample of bars and taverns and surveyed bartenders before and after a statewide prohibition on smoking in such establishments. Interviewers assessed lower respiratory tract symptoms, sensory irritation symptoms (eye, nose or throat irritation), ETS exposure, personal smoking, and recent upper respiratory tract infections. Spirometry was also performed. Fifty-three of 67 eligible bartenders were interviewed; all reported workplace ETS exposure at baseline. Respondents reported a reduction in median weekly workplace ETS exposure from 28 hours pre-to 2 hours post-intervention ($p<0.001$). One-quarter of bartenders were active smokers, a number that was unchanged post-intervention. Of the 41 (77%) respondents who initially reported sensory irritation symptoms, 32 (78%) reported resolution of symptoms post-intervention ($p<0.001$). The authors concluded that "…establishment of smoke-free bars and taverns was associated with a rapid improvement of respiratory health."

Raynal et al. (1995) studied 375 office employees in a large, open-plan smoking-permitted building and 26 individuals from a building in which no smoking was permitted. Participants were administered a questionnaire regarding a variety of symptoms which improved outside of the work environment during the twelve months prior to survey. These included mucous membrane (eye, nose, throat) irritation, lethargy, flu-like illness, chest tightness and "difficulty breathing." A composite score ("Personal Symptom Index" or "PSI") was constructed for each individual, utilizing adjustment for demographic variables. Active smoking histories were taken, and both exhaled breath carbon monoxide (CO) and salivary cotinine levels measured for validation purposes. Workplace temperature, humidity and airflow were measured in 5 locations each, and vapor-phase nicotine levels in 23 different sub-areas of the main workplace.

The sample of potentially exposed workers was 70% female and 25% active smokers; the unexposed group was younger and more predominantly male, but comparable in their active smoking rate (19%). Eleven subjects self-reported as non-smokers but had salivary cotinine levels greater than 15 ng/mL; these respondents were analyzed separately from those whose smoking histories and biomarkers were concordant. Among validated non-smokers, there was a

positive association between [area] environmental nicotine measurements and both reported symptoms ($r = 0.165$; $p<0.01$) and saliva cotinine levels ($r = 0.313$; $p<0.001$). Among the various symptoms reported, eye nose and throat irritation were most closely related to environmental nicotine levels. Active smokers reported fewer symptoms than did non-smokers for a given [area] nicotine measurement. No symptom correlations were found with variations in temperature, humidity, or airflow. The authors indicated that the small size of the control group may have obscured differences in composite scores (the "Building Symptom Index" or "BSI") between the main study and control groups. However, the relationship between symptoms and ETS exposure was based upon a cross-sectional comparison within the main workplace, and was not affected by sample size considerations.

6.4.2.3. Controlled Human Exposure Studies of Sensory Irritation

Investigators from the laboratory of Dr. Rebecca Bascom completed a total of four studies that were not referenced in the 1997 Cal/EPA report (Bascom *et al.*, 1995& 1996; Kesavanathan *et al.*, 1996; Willes *et al.*, 1998). These build upon the work described in the original two reports that were reviewed in the earlier Cal/EPA report (Ehrlich *et al.*, 1996 and Ng *et al.*, 1993), and address dose-response considerations, alternative measures of nasal patency (acoustic rhinometry rather than rhinomanometry), and alternative physiologic endpoints (nasal mucociliary clearance rather than nasal patency). In addition, three other controlled human exposure studies were identified which emphasized upper airway endpoints (Nowak *et al.,* 1997b; Walker *et al.*, 1997; Junker *et al.*, 2001). These investigations are summarized below.

Table 6.42 Controlled Human Exposure to ETS and Sensory Irritation

Reference Country	Study Description	Exposure to smoke	Findings and OR (95% CI)	Comments
Junker *et al.* 2001 Switzerland	3 studies: emissions by smoking machine; odor threshold; respiratory irritation in 24 women.	Sidestream (SS) at 4.4-431 μg/m^3 $PM_{2.25}$ in chamber	Eye, throat and nasal irritation elevated even at lowest SS levels corresponding to dilution vol of >3000 m^3/cigarette	Odor threshold much lower than typical ETS measured in field. Symptoms at levels much lower than previously reported.
Willes *et al.* 1998 US	Upper airway symptoms in 14 ETS-S and 9 ETS-NS.	Sidestream 15 ppm CO for 2 hr	Nasal symptoms and NAR rose significantly with exposure but no significant differences in mean response between ETS-S and ETS-NS.	ETS-related NAR increases greatest in ETS-S group. Exposure validated by urinary cotinine.
Nowak *et al.* 1997b Germany	Exposed 10 asthmatics to sidestream smoke. Evaluated nasal lavage (NL) and lower airway inflammation.	Sidestream 22 ppm CO for 3 hr on alternate days	Smoke exposure gave significant increase in eye, nose and throat irritation. NL not different before vs after.	Based on NL, 3 hr ETS not significant stimulant of inflammation in upper airway.
Walker *et al.* 1997 US	Assessed behavior and respiratory symptoms after expo to 5 levels of ETS in 17 men.	90 min expo to 5 levels of ETS (0.25-3 ppm CO	Expo-related increases in eye irritation, odor annoyance, nose and throat irritation. Trend of increasing anxiety and anger with ETS.	Changes in symptoms, respiration and behavior: increasing with higher expo.
Bascom *et al.* 1996 Kesavanathan *et al.* 1996 US	Nasal mucociliary clearance (NMC) in 13 ETS-sensitive (ETS-S) and 16 non-sensitive (ETS-NS) adults.	Sidestream 1, 5, 15 ppm CO, for 2 hr	Symptoms increased with exposure. Nasal volume decreased in exposure-dep. manner for ETS-S Nasal airway resistance (NAR) different at 1, 5 ppm for ETS-S vs -NS	Complex differences in responses to SS by ETS-S vs ETS-NS. Subjective congestion correlated with NAR in ETS-S but with nasal volume in ETS-NS
Bascom *et al.* 1995 US	Nasal mucociliary clearance (NMC) in 6 ETS-sensitive (ETS-S) and 6 non-sensitive (ETS-NS) adults.	Sidestream for 60 min on 2 days (CO 15 ppm)	Nasal clearance of radiotracer slower in ETS-S after smoke exposure.	Small study and marked heterogeneity in NMC response to smoke.

ETS-NS: ETS-nonsensitive ; ETS-S : ETS-sensitive ; NAR : nasal airway resistance: NL: nasal lavage; SS: sidestream smoke

Junker et al. (2001) conducted three separate substudies relating to ETS. The first was an emissions study, in which they found that machine-smoked cigarettes yielded significantly more VOCs and CO, but lower particulate mass, than had previously been documented. The second was an "odor threshold" study using an olfactometer, in which 18 female non-allergic non-smoking subjects detected SS odor in an ascending series, method of limits paradigm. The mean odor threshold corresponded to fresh air dilution volume of > 19,000 m^3 per cigarette, over 100

times more than had previously been suggested for acceptable indoor air conditions. The third substudy was a whole-body ("chamber") study, in which 24 female subjects breathed SS over a wide concentration range (4.4 – 431 $\mu g/m^3$ $PM_{2.25}$), the lowest of which corresponded to the level yielding odor detection in 95% of the threshold trials. Eye, throat and nasal irritation, arousal, and annoyance were significantly elevated at the lowest SS exposure level, corresponding to a fresh air dilution volume of > 3,000 m^3 per cigarette. The authors pointed out that odor threshold concentrations for SS are three and more orders of magnitude lower than typical ETS concentrations measured in field settings, and that symptoms appeared at one order of magnitude lower SS concentrations than previously reported. They concluded that acceptable air quality for nonsmokers in smoking-permitted buildings may only be achievable with complete physical separation of smokers and non-smokers.

Willes et al. (1998) studied 23 subjects, 14 ETS-S and 9 ETS-NS, with controlled exposures on two separate days to clean air or SS (15 ppm CO equivalent times two hours). Eight of fourteen ETS-S subjects (57%) were judged to be atopic by skin testing, and an even greater proportion of the ETS-NS subjects (78%) had evidence of allergies. In terms of upper airway endpoints, subjects rated symptoms and had nasal airway resistance (NAR) measured by posterior rhinomanometry both pre- and post-exposure. Nasal lavage (NL), on the other hand, was limited to post-exposure. Urinary cotinine levels were used to validate exposure. Following SS exposure nasal symptoms increased and NAR rose significantly. Although 7 of the 8 subjects with the greatest ETS-related increases in NAR were in the ETS-S group, the two groups did not differ significantly in their mean response to ETS challenge. Nasal lavage markers, on the other hand, including total cell counts, neutrophils, and albumin, were unaffected by ETS exposure.

Nowak et al. (1997b) exposed 10 mild asthmatics to sidestream smoke at 22 ppm CO-equivalent for 3 hours, with control (clean air) exposure on separate days. Although the emphasis of this study was the lower airway (see Section 6.1.1.5), nasal lavage (NL) fluid was also obtained 30 minutes before and 30 minutes after smoke exposure. NL fluid was analyzed for histamine, albumin, eosinophilic cationic protein, myeloperoxidase, hyaluronic acid, and tryptase. Sidestream smoke exposure resulted in significantly greater increases in self-reported eye, nose and throat irritation compared with clean air exposure ($p < 0.05$). NL mediators post-SS exposure were not significantly different from pre-challenge or post-sham values, however. The

authors concluded that a 3-h ETS exposure was not a significant pro-inflammatory stimulus in the upper airway.

Walker et al. (1997) exposed 17 non-smoking, non-allergic white male subjects to clean air and five different experimentally generated ETS levels between 58 and 765 $\mu g/m^3$ total respirable particles (0.25-3 ppm CO over background). Sessions lasted 90 minutes with a 50-min "plateau" period. Endpoints included symptom reporting, respiratory behavior, eye blink rate, cognitive performance, and mood state. Subjective eye irritation, eye dryness, odor, annoyance, and lack of air quality acceptability all rose significantly at the lowest ETS level employed, and increased monotonically with concentration thereafter. Nose and throat irritation were significantly elevated at or above the second ETS exposure level (0.5 ppm CO over background). Respiratory changes consisted of decreased respiratory rate and increased tidal volume, with minute ventilation staying relatively constant. Ventilatory changes occurred at all ETS exposure levels, without evidence of a dose-response relationship. Significant increases in eye blink rate occurred at the highest exposure level only. There were no significant exposure-related changes in cognitive performance, but a trend toward increased anxiety and anger – and decreased curiosity – which was significant at the highest exposure level. The authors argued that even the lowest ETS exposure level employed in this experiment was higher than real-life ETS exposures, and that 80% of individuals would be expected to find air containing ETS at 63 $\mu g/m^3$ total respirable particles unacceptable.

Bascom et al. (1996) and *Kesavanathan et al. (1996)* studied 13 ETS-S and 16 ETS-NS subjects exposed to "low-to-moderate" SS levels (1, 5, and 15 ppm CO times 2 hours). A high proportion of subjects in both groups (69% of ETS-S and 50% of ETS-NS) had skin test reactivity to one or more aeroallergens. Objective endpoints included both nasal airway resistance (NAR) measured by posterior rhinomanometry, and nasal cross-sectional area/volume by acoustic rhinometry (AR). In general, postexposure symptoms increased monotonically with exposure level, with eye irritation and odor reaching significance at a lower exposure level (1 ppm CO) than nasal congestion, rhinorrhea, or cough (15 ppm) (see Table 6.43). Differential responses by historical sensitivity status were evident for NAR at 1 and 5 ppm – but not at 15 ppm. The pattern of differences was complex, in that the ETS-NS group showed more objective nasal congestion at 1 ppm and the ETS-S group showed more congestion at 5 ppm. The pattern of differences for AR

was even more complex, depending upon the portion of the tracing targeted (anterior, mid-, or posterior nasal cavity). In ETS-S subjects, nasal volume decreased in a dose-dependent manner. ETS-NS showed a qualitatively complex response pattern, with significant dimensional reductions in mid- and posterior nasal at 1 ppm CO but not at 5 ppm CO, and reductions in posterior nasal volume at 15 ppm CO. Kesavanathan *et al.* (1996) formally compared the endpoints of NAR and AR from this dataset in terms of coefficient of variation and correlation between symptoms and instrumental findings. In this latter regard, baseline subjective congestion correlated with NAR in ETS-S subjects, but with AR in ETS-NS subjects.

Bascom et al. (1995) studied nasal mucociliary clearance (NMC) in 12 healthy adults, half of whom had a history of ETS sensitivity and an objective, congestive response to a controlled challenge to ETS (ETS-S) and half non-sensitive (ETS-NS). Investigators exposed subjects to either air or sidestream tobacco smoke (SS) on 2 separate days, at least a week apart, in a climate-controlled chamber. Exposures lasted 60-min and the level of SS was regulated to a carbon monoxide concentration of 15 ppm. Roughly an hour after the exposure, 99 mTc-sulfur colloid aerosol was introduced nasally and serial counts were measured with a scintillation detector over the following hour. As a group, ETS-NS subjects showed more rapid clearance of the radiolabeled tracer than did ETS-S subjects. This group difference was based on half (3 of 6) ETS-S subjects, who showed marked inhibition of NMC. This subgroup did not differ significantly from the other ETS-S subjects with regard to age, gender, or allergy status. The authors acknowledged a marked heterogeneity in response of NMC to SS exposure, and the fact that multiple factors may govern the response. If present, slowed NMC could predispose individuals to respiratory tract infections.

Table 6.43 Symptomatic Responses to Sidestream Smoke - ETS Sensitive Subjects* Bascom *et al.*, 1996.

Symptom	1 ppm CO	5 ppm CO	15 ppm CO
Headache	0.2	0.5[a]	1.1[a]
Eye Irritation	0.9[c]	1.8[e]	3.3[e]
Nose Irritation	0.5[a]	0.3[c]	2.2[e]
Nasal Congestion	0.4	0.2	1.3[d]
Rhinorrhea	0.4[a]	0.1	1.3[b]
Sneezes	0	0.1	0.2
Odor Perception	1.2[e]	2.2[e]	3.5[e]
Chest Tightness	0	0.1	0.8
Cough	0.1	0.2	1.0[a]

Mean mid-exposure values of symptom response scores: [a]p<0.05, [b]p<0.01, [c]p<0.005, [d]p<0.001,[e]p<0.0001

6.4.2.4. Miscellaneous Health Studies

Avunduk et al. (1997) conducted an animal experiment to identify the subacute effects of tobacco smoke exposure on the conjunctiva. The authors exposed 12 male albino rats to mainstream cigarette smoke for 2 hours per day over a 60 day period; conjunctival histology was compared with a like group of control (air-exposed) animals. Total particulate levels were approximately 1200 $\mu g/m^3$. Both light and electron microscopy was employed. The authors found that in the exposed animals the conjunctivae were thinned and atrophied, and that microvillous projections and desmosomal connections were absent in comparison with the control conjunctivae. They concluded that the pathology appeared to be a non-specific irritant effect. Extrapolation of these results to humans exposed to ETS would require quantitative factoring for: 1) sidestream vs. mainstream smoke exposure; 2) lower-dose extrapolation; and 3) interspecies extrapolation.

Lakshmipathy et al. (1996) were interested in laryngeal irritability – as manifest by intraoperative laryngospasm – as a function of ETS exposure in children. To study this, they performed a retrospective analysis of 310 consecutive pediatric patients who underwent an outpatient elective ear, nose, and throat or urologic surgery using halothane general anesthesia in a hospital and ambulatory surgical center. Laryngospasm was identified by medical record review, and cases were excluded if there was a history of asthma, bronchopulmonary dysplasia, pneumonia, or viral upper respiratory symptoms within the two weeks prior to surgery. To determine ETS exposure status, patients' families were questioned within one week after surgery, and the number of smokers in each child's household was determined. A relative risk was then calculated (data treated as retrospective cohort). Ninety-six children were identified with

household ETS exposure and 214 without; the two groups were comparable in terms of gender and mean age. Nine of the exposed (9.4%) and two of the unexposed (0.9%) children developed laryngospasm. The authors stated: "…the relative risk for developing laryngospasm was 10 times higher in the ETS-exposed patients compared with the non-ETS-exposed group (RR = 10.0; 95% CI 2.2; 45.6; $p < 0.001$)," and concluded that "…ETS exposure is a strong risk factor for laryngospasm in infants and children during general anesthesia." An alternative analysis of the data would treat the data as cross-sectional, and would examine an odds ratio (OR) instead of a relative risk. Using this statistical paradigm, the OR=10.97, with a similar statistical conclusion.

6.4.2.5. Industrial Hygiene Surveys

Liu et al. (2001) surveyed 111 municipal buildings in California with 118 designated smoking areas during the years 1991 to 1994, before the institution of no-smoking ordinances for public buildings in the state. In terms of physical separation, they found that 41% of designated smoking areas lacked separation from adjacent non-smoking areas, and only 31% were separated with walls that did not terminate in "false ceilings." In terms of ventilation, 72% of designated smoking areas had no separate exhaust fan, and only 25% had exhaust fans that led directly to the outside. Overall, less than half of designated smoking areas (38%) had exhaust ventilation that was not recycled into the main building system. Based upon indoor measurements of airborne nicotine and tracer gas (SF_6) studies, the authors concluded that the most effective reduction in cross-contamination required a combination of physical separation, exhaust to outside, and no air recirculation. These conclusions were largely rendered moot in California with the implementation of AB-13 in 1995.

6.4.2.6. Summary of Sensory Irritation and Annoyance, and Dose-response Considerations

A number of newer studies reinforce the role of ETS in the genesis of mucous membrane irritative symptoms ("sensory irritation"). These include cross-sectional surveys within or between smoking-permitted workplaces (Raynal *et al.*, 1995; Mizoue *et al.*, 2001; Jones *et al.*, 2001) and longitudinal studies of occupational cohorts before and after the institution of indoor smoking restrictions (Eisner *et al.*, 1998; Wieslander *et al.*, 2000). In addition to epidemiological surveys, a number of newer controlled human exposure studies were identified. In general, these studies have utilized lower provocative exposure levels than did earlier studies.

For example, Bascom's group evaluated sidestream smoke effects at CO-equivalent exposures between 1 – 15 ppm (vs. an earlier provocative level of 45 ppm – Bascom *et al.*, 1991). To generalize from the studies reviewed here, on a dose-response basis, subjective complaints of odor, annoyance, and eye irritation appear at lower SS concentrations than do nose and throat irritation, rhinorrhea, and cough (with the former appearing as low as 1.0 ppm CO-equivalent). Objective nasal congestion among exposed subjects has been demonstrated at exposure levels as low as 1.0 ppm CO-equivalent (Bascom *et al.*, 1996). Exposures for as long as 3 hours to SS at 15-22 ppm CO-equivalent, however, did not produce an inflammatory response in nasal lavage fluid (Willes *et al.*, 1998; Nowak *et al.*, 1997b).

Walker and colleagues (1997) documented increases in eye blink rate with SS exposures indexed at 765 $\mu g/m^3$ total respirable particles (3 ppm CO over background), whereas Junker *et al.* (2001) observed no such changes at 431 $\mu g/m^3$. This compares with earlier work by Muramatsu *et al.*, 1983), who documented both subjective eye irritation and increases in blink rate at SS exposure levels greater than 1.3 ppm CO. A problem that is immediately apparent is the lack of a universally accepted surrogate measure of ETS exposure. The majority of studies to date have included CO as a surrogate measure, either alone (Bascom *et al.*, 1995, 1996; Willes *et al.*, 1998) or in conjunction with respirable particulate matter (Nowak *et al.*, 1997b; Walker *et al.*, l997). One study analyzed here, however, utilized only PM as an exposure surrogate (Junker *et al.*, 2001). An integrated risk assessment utilizing data from all of these studies would require a conversion factor between the two metrics, which have widely varying ratios both within and between different studies.

Another dimension of a subset of the studies reviewed here (i.e., those conducted by Bascom and colleagues) is the identification of "historically ETS-sensitive" and "ETS-nonsensitive" subject subgroups prior to exposure. In their original 1991 study, Bascom *et al.* documented augmented reactivity to SS (objective nasal congestion) in the former group compared to the latter. This apparent differential sensitivity has been an inconstant feature of subsequent studies by this group. A potential confounding variable, however, is the fact that, from study-to-study, varying proportions of the two subgroups have documented allergies (i.e., skin test positivity to one or more common aeroallergens). Since allergic inflammation has been proposed as a neuromodulator, up-regulating both afferent and efferent portions of respiratory tract reflexes,

studies stratifying on self-reported ETS sensitivity might profitably control for the presence of recognized allergic disease in research subjects (Shusterman *et al.*, 1998; Togias, 2000; Undem *et al.*, 2000).

A final note deals with ETS-related annoyance and the concept of "acceptable" air quality. As information disseminates to the general public regarding acute and chronic ETS-related health effects, attitudes (and risk perception) change. Cognitive biases regarding the health significance of odor sources appear to affect the likelihood of symptom reporting, both in field and in laboratory settings (Shusterman *et al.*, 1991; Dalton *et al.*, 1997). Thus, estimates of indoor air quality "acceptability" are specific to the experimental group employed, and may show trends over time, with lower ETS exposure levels likely to be tolerated by an informed (and concerned) public.

The overall conclusions of OEHHA staff regarding the sensory impact of ETS exposure remains unchanged from that offered in the 1997 document:

> "ETS exposure produces a variety of irritative symptoms involving the upper respiratory tract; increasingly, these endpoints are able to be objectively documented and quantified. In addition to irritation, odor annoyance may detract significantly from subjective wellbeing and productivity among building occupants. Experimental studies conducted by investigators familiar with building ventilation practice suggest that, short of prohibiting indoor smoking, protection of nonsmokers against both sensory irritation and odor annoyance can only be achieved through relatively extreme engineering measures."

6.5. Chronic Health Effects in Adolescents and Adults

6.5.1. Pulmonary Function Changes and Respiratory Symptoms

In its 1997 report, Cal/EPA reviewed a total of twenty studies examining the health endpoints of chronic chest symptoms, pulmonary function changes and frank chronic obstructive pulmonary disease (COPD) in adults exposed to ETS. Eleven of these studies had previously been reviewed by the Surgeon General's Office (U.S. DHHS, 1986), NRC (1986), or the U.S. EPA (1992); an additional nine studies were reviewed by Cal/EPA staff. Based upon their review, Cal/EPA staff concluded:

"…ETS exposure may make a significant contribution to chronic respiratory symptoms in adults. In conjunction with reports of acute lower respiratory tract symptoms among individuals with pre-existing asthma (see Section 6.1.1), the small differences in lung function found in epidemiological studies are a basis for concern and further study."

6.5.1.1. Newer Epidemiological Data

This section reviews the epidemiological evidence bearing on the question of chronic exposure to ETS, lung function, and chronic respiratory symptoms in adults. In this update, the literature has been divided between studies describing adult chronic respiratory symptoms and/or pulmonary function changes as individual findings (reviewed here) and studies of adult-onset medical diagnoses of asthma and/or COPD (reviewed in Section 6.2.1). In the former category, we identified a total of five additional relevant studies, which are summarized below and in Table 6.50

Table 6.50 Respiratory Function Changes vs ETS Exposure

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Kunzli *et al* 2000 Switzerland	Cross-sectional Spirometry vs ETS n = 3534 nonsmokers	Home and work by questionnaire	Sig. decrement in FEV_1 & FEF_{25-75} in asthmatic women	ETS (hr/d and years) predicted pulmonary decrements. Possible recall bias.
Berglund *et al* 1999 US	Longitudinal cohort: Spirometry n = 1391 Chronic airway disease AHSMOG)	Home and work by questionnaire	Years living with smoker predicted chronic obstructive pulmonary changes	Obstruction as ratio FEV_1/Vcmax < 65% or FEV_1 < 75% of predicted
Abbey *et al* 1998 US	Longitudinal cohort: Spirometry vs air pollutants n = 1391 (AHSMOG)	Home and work ETS assessed by questionnaire	ETS not significantly associated with FEF or FEV_1/FVC. ↑PEF lability in males.	↑PEF lability from work ETS only seen in males.
Mannino *et al* 1997 US	Cross-sectional: respiratory disease exacerbation n = 43,732	Home, work: self report	Disease exacerbation 1.44 (1.07; 1.95)	Chronic bronchitis, sinusitis, emphysema worsened by ETS.
Jaakkola *et al* 1996 Canada	Longitudinal cohort: 15-40 yr old non-smokers. 8 yr follow-up for respiratory symptoms. n = 117	Home and work ETS assessed yearly by questionnaire	New onset dyspnea associated with ETS. Wheeze and cough elevated but not significantly.	Small sample size and no objective ETS measures

FEF_{25-27} forced expiratory flow at 25-75% of vital capacity; FEV_1 forced expiratory volume in one second; FVC forced vital capacity ; MMEF maximum mid-expiratory flow; PEF peak expiratory flow

Kunzli et al. (2000) focused on workplace ETS exposure in a cross-sectional sample of 17,300 Swiss adults age 18-60 years. The authors successfully recruited 9,651 for questionnaire survey and spirometry, of whom 3,534 yielded lifetime non-smoking histories. In this subgroup, ETS exposure histories were obtained over the one-year prior to sampling including number of smokers at home, presence or absence of smokers at work, and total hours of ETS exposure per day. Researchers also asked about degree of "disturbance" [annoyance] due to ETS exposure. Atopy was indexed by a semiquantitative blood test for total IgE (Phadiatop®). Other covariates included age, gender, and educational level. Of the 3,534 in the final sample, 61% were female (a fact that the authors attributed to the lower prevalence of active smoking in females), and 10% were asthmatics. Fifteen percent of females reported ETS exposure at work (compared to 22% of males), and 18% and 12% of females and males, respectively, reported ETS exposure at home. Restricting the analysis to individuals with no household ETS exposure, the authors found that workplace ETS exposure was associated with a significant decrement in FEV_1 and FEF_{25-75} in asthmatic women only. Semi-quantitative measures of ETS exposure (hours/day and total years exposed) predicted decrements in one or both of the above pulmonary function measures. The authors pointed out that an inherent weakness of the study is the potential for recall bias among individuals with asthma and/or female respondents (although females did not report significantly higher subjective annoyance than did males), as well as the lack of objective measures of ETS exposure.

Berglund et al. (1999) reported on a sub-cohort study from the AHSMOG study (see Abbey *et al*., 1998, described below). From 3,091 surviving and 1,870 eligible study participants, 1,510 were examined and 1,391 met criteria for adequacy of spirometry data, current non-smoking status, and lack of other (non-obstructive cardiopulmonary) health conditions. Spirometry was performed according to ATS guidelines; "obstruction" was defined as either a ratio of $FEV_1/VCmax < 65\%$ or $FEV_1 < 75\%$ of predicted. "Chronic airway disease" (CAD), including asthma, chronic bronchitis, and emphysema, was defined based upon both symptom data and reported physician diagnosis. Covariates accounted for in the analysis included age, gender, family history of CAD or hay fever, and childhood respiratory illnesses. In a multivariate logistic regression analysis, the authors found that obstructive pulmonary function changes, as defined above, were significantly more common as a function of ETS exposure, the latter being defined as years living with a smoker as an adult. Other ETS exposure indices, including years

working with a smoker and years living with a smoker as a child, did not predict pulmonary obstructive changes.

Abbey et al. (1998) reported on a long-term cohort study of 6,338 non-smoking non-Hispanic white Seventh-day Adventists originally begun in 1977 (Adventist Health Study of Smog, or AHSMOG study). The focus of this study was ambient air pollutants, with self-reported ETS exposure at home or work being a covariate (along with age, years of smoking prior to 1977, workplace dust and/or exposure, years of education, body mass index, exercise habit, housing density, housing heating source, and % of time spent outdoors). Of surviving study participants, 1,914 met eligibility criteria for age (<80 years), residence (within 20 miles of an air monitoring station), and participation (having completed questionnaires in 1977, 1987, and 1992). Of these, 1,510 were willing and/or able to be examined in clinic in 1993, and 1,391 met criteria for adequacy of spirometry data, current non-smoking status, and lack of other (non-obstructive cardio-pulmonary) health conditions. ETS exposure was ascertained by questionnaire and spirometry was performed according to ATS guidelines. Participants were further instructed to obtain pulmonary peak expiratory flow (PEF) measurements at home, four times per day for one week. Peak flow "lability" was defined as the difference between the highest and lowest values of PEF divided by the mean value for a given day. In a multivariate regression model, neither home nor workplace ETS exposure was associated with significant decrements in percent predicted FEV_1 or % FEV_1/FVC. Self-reported ETS exposure at work was significantly associated with increased PEF lability in male subjects only.

Mannino et al., 1997. In an analysis of 43,732 adults completing the Health Promotion and Disease Prevention supplement of the 1991 National Health Interview Survey, the cross-sectional association between self-reported ETS exposure at home or work and the risk of "chronic respiratory disease exacerbation" was examined. This study outcome was defined as activity limitation or a physician visit due to a chronic respiratory disease: asthma, chronic bronchitis, emphysema, or chronic sinusitis. Among never-smokers, ETS exposure was associated with an increased risk of chronic respiratory disease exacerbation (OR 1.44; 95% CI 1.07; 1.95). Although the population-based sampling and careful control of confounding are study strengths, the relationship between ETS exposure and asthma alone cannot be clearly elucidated from the published study.

Jaakkola et al., 1996. In a cohort study of respiratory health in "young adults" (aged 15-40 at time of initial recruitment), Jaakkola *et al.* conducted an eight-year follow-up of a subset of 117 never-smoking participants. ETS exposure and respiratory symptoms were determined on year-by-year basis using the American Thoracic Society standardized questionnaire. Covariates for which adjustment was made in multivariate analysis included age, gender, atopy, and the presence of respiratory symptoms at baseline. ETS exposure was ascertained separately for the home and workplace, and a total exposure index was constructed. Overall, 62% of subjects reported regular exposure to ETS either at work or at home during the study period. A significant association was found between total ETS exposure index and new-onset dyspnea during study period (OR 2.37/10 cigarettes/day; 95% CI 1.25; 4.51). Central estimates of odds ratios for new-onset wheeze and cough (but not phlegm) were also elevated, but not significantly. The strengths of this study were its longitudinal design and use of a standardized questionnaire. The weaknesses include the lack of objective indices of ETS exposure, as well as the small sample size. A companion study of pulmonary function by Jaakkola *et al.* (1995) in the same cohort was reviewed in the 1997 Cal/EPA document, and failed to demonstrate significant pulmonary function decrements over the above follow-up period.

6.5.1.2. Summary of Epidemiological Data – Pulmonary Function and Symptoms.

Newer epidemiological data support a small but potentially biologically significant effect of ETS exposure on pulmonary symptoms and function in adults. Two of three pulmonary function studies (Berglund *et al.*, 1999 and Kunzli *et al.*, 2000) demonstrated significant changes in spirometric parameters (FEV_1 % of predicted, FEV_1/VC, and FEF_{25-75}) among all or subsets of ETS-exposed subjects compared to controls. The third study (Abbey *et al.*, 1998) did not replicate these findings, but did find more lability in ambulatory peak flow measurements among males with self-reported workplace ETS exposure. This latter finding is consistent with a longitudinal study of bartenders by Eisner *et al.* (1998), in which the prevalence of respiratory symptoms (wheeze, cough, and phlegm production) decreased - and pulmonary function parameters (FEV_1 and FVC) increased - following the institution of a smoking ban in bars and taverns. Finally, in a small cohort study of young adults, self-reported ETS exposure at work or home was significantly associated with the development of at least one chronic respiratory symptom (Jaakkola *et al.*, 1996). Collectively, these data suggest that ETS exposure may play a

role in the genesis of chronic respiratory symptoms and produce small, but measurable, decrements in pulmonary function.

6.5.1.3. Other Respiratory Effects

Blanc et al., 1999. In the Swedish component of the European Community Respiratory Health Survey, Blanc and colleagues examined the cross-sectional impact of self-reported workplace ETS exposure among 2,065 adults (20-44 years). Regular workplace ETS exposure was associated with a greater risk of respiratory-related work disability (prevalence ratio 1.8; 95% CI 1.1; 3.1), defined as self-reported change in job or leaving work due to affected breathing. Moreover, workplace ETS exposure was related to a greater risk of work-associated symptomatic asthma, defined as self-reported asthma, airway hyper-responsiveness, and work-related chest tightness or wheezing (PR 1.7; 95% CI 0.9; 3.3). Because this study focused on workplace factors, home and other sources of ETS exposure were not examined.

6.5.1.4. Animal Model of Allergic Sensitization.

Rumold et al. (2001) used a murine model to test whether exposure to side stream smoke (SS; a surrogate for ETS) can induce allergic sensitization to inhaled ovalbumen (OVA) in both high (BALB/c) and low (C57BL/6) IgE-responsive mice. Adult mice (6-8 wks) were exposed on 10 consecutive days to either saline or nebulized 1% OVA for 20 min., SS from 5 cigarettes for 1 hr, or SS for 1 hr followed by OVA for 20 min. Twenty days later the mice were re-exposed to 1% OVA for 20 min. Bronchoalveolar lavage (BAL) was performed 24 hours later for determination of cytokines in BAL fluid. IgE and IgG1 levels were measured in peripheral blood.

By day 18 following initiation of exposure (8 days following cessation), both total serum and OVA-specific IgE levels were significantly elevated in both high and low responders exposed to OVA/SS compared to OVA alone ($p<0.01$). Similarly IgG1 levels but not IgG2a were significantly elevated in this group ($p<0.01$). Cytokine induction (IL-5, GM-CSF, IL-2) was observed after OVA re-exposure in BAL fluid from mice exposed to SS/OVA but not in mice exposed to OVA alone. Mice exposed to SS/OVA but not OVA alone developed eosinophilia, had significantly less IFN-γ, and had increases in the Th2 cytokine IL-5. SS alone resulted in elevated GM-CSF and IL-2 upon re-exposure. The production of specific allergic antibodies to

inhaled allergens is characteristic of the sensitization phase of reactive airway disease. These experiments indicate that ETS has the capacity to alter lung homeostasis and augment allergic sensitization to otherwise innocuous allergens.

6.5.1.5. Mechanisms of Airway Effects.

In its 1997 review, Cal/EPA staff outlined several potential mechanisms whereby ETS might produce obstructive airway disease (as in emphysema) and/or mucous hypersecretion (as in chronic bronchitis). These included "…cigarette smoke-induced bronchopulmonary inflammation, induction of airway hyperresponsiveness, inhibition of mucociliary clearance (and other antimicrobial defenses), goblet cell hyperplasia, release of proteolytic enzymes from inflammatory cells, and possibly inhibition of antiproteases..." Newer data are available on two of these mechanisms.

Borchers et al., 1999. In an in vitro study, Borchers and collegues exposed human lung carcinoma cells to acrolein, an irritant found in ETS. The cells produced significantly elevated levels of messenger RNA coding for two different mucins, MUC5AC and MUC5B. Mucins are an essential component of airway mucus, and the authors make the point that increased mucin production by airway epithelial cells translates clinically into mucous hypersecretion, as seen in chronic obstructive pulmonary disease.

von Ehrenstein et al., 1999. In humans, inhibition of anti-proteases has emerged as a credible mechanism for diminished lung function, at least in children. In a meeting abstract, Von Ehrenstein *et al.* reported on a survey of nearly 1,256 schoolchildren on whom parental questionnaire, spirometry, and plasma levels of α1-antitrypsin were obtained. Both parentally-reported ETS exposure and low α1-antitrypsin levels were associated with slightly decreased lung function parameters (% predicted FEV_1 and FVC). The combination of both risk factors was synergistic, producing significantly lower PFT values. This type of investigation - known as "molecular epidemiology" - will be useful in identifying susceptible subpopulations.

6.5.2. Asthma Induction in Adolescents and Adults

6.5.2.1. Asthma Induction in Adolescents and Adults – Recent Epidemiological Studies

Table 6.51 ETS and New-onset Asthma in Adolescents and Adults

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Eagan *et al.* 2004 Norway	Cohort 11 yr Asthma follow-up n = 2,819	Self-report - Pre- and postnatal maternal smoking Maternal smoking All childhood ETS	Incident adult asthma OR 3.5 (1.8; 6.8) Attributable fraction 16.9 % (4.8; 27.4) 26.0 (0.03; 45.2)	In utero or childhood ETS from mother and others increased risk of adult-onset asthma
Jaakkola *et al* 2003 Finland	Case-control Population-based 239 asthma 487 ctrl	Self report- Home Work Trend 10 cig/day Total Trend 10 cig/day	Previous 12 months 4.77 (1.29; 17.7) 2.16 (1.26; 3.72) 1.44 (1.03; 2.01) 1.97 (1.19; 3.25) 1.33 (1.02; 1.75)	Clinically diagnosed new asthma more strongly associated with recent vs lifetime ETS
Iribarren *et al* 2001 US	Cross-sectional Asthma or hay-fever. n = 47,721	Self report - total ETS. Asthma, hayfever	Diagnosed 1.22 (1.11; 1.34) 1.14 (1.06; 1.24)	Risk of physician-diagnosed asthma or hayfever increased
Larsson *et al* 2001 Sweden	Cross-sectional Asthma n = 8,008	Self report. ETS in childhood vs none. Asthma family history	Diagnosed adult asthma 7.6 vs 5.8% p=0.035 1.82 (1.28; 2.58)	ETS in childhood or with family history of asthma increased risk
Janson *et al* 2001 Europe	Cross-sectional Asthma 20-48 yr n = 7,882	Self report - Home Work	Current asthma 1.14 (0.68; 1.90) 1.90 (1.25; 2.88)	Home ETS defined as living w/smoker Work: regular smoking in work area
Thorn *et al* 2001 Sweden	Case-control Asthma 20-50 yr 174 cs; 870 ctrl	Self report – home during or prior to asthma onset	Diagnosed onset Male: 4.8 (2.0; 11.6) Female: 1.5 (0.8; 3.1)	Increased risk only among neversmokers; not current or ex-
McDonnell *et al* 1999 US	Cohort 15 yr Asthma follow-up. n = 3091	Self report work Men Women	Asthma N.S. 1.21 (1.04; 1.39)	At 15 yr follow-up, only females had increased risk
Kronqvist *et al* 1999 Sweden	Cross-sectional Asthma and allergic rhinitis. n = 1,015	Self report - total ETS.	Respiratory symptoms: NS	No association found with ETS but no risk estimates given
Hu *et al* 1997b US	Cohort 7th graders Asthma at 20-22 n = 2,041	Parental report Maternal ETS Paternal ETS	Diagnosed as adult 1.8 (1.1; 3.0) 1.6 (1.1; 2.4)	ETS at baseline raised risk of asthma in adulthood 7 yr later
Flodin *et al* 1995 Sweden	Case-control Asthma ≥ 20 yr 79 cs; 304 ctrl	Self report – prior 3 yr Home Work	Diagnosed onset 0.9 (0.5; 1.5) 1.5 (0.8; 2.5)	Study doesn't support association of asthma with ETS

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Greer *et al* 1993 US	Cohort 10 yr Asthma follow-up n = 3917	Self report work	Asthma 1.5/10 yr (1.2; 1.8)	Duration of working with smoker increased risk at 10 yr follow-up

The 1997 OEHHA report reviewed studies that evaluated the relationship between ETS exposure and chronic pulmonary disease among adults, including asthma. Based on this review, the report concluded that "…ETS exposure may make a significant contribution to chronic respiratory symptoms in adults." Although the report reviewed five studies that supported an association between ETS exposure and adult asthma (Dayal *et al.*, 1994; Greer *et al.*, 1993; Leuenberger *et al.*, 1994; Ng *et al.*, 1993; Robbins *et al.*, 1993), no specific conclusions were articulated about asthma *per se*.

Eagan et al., 2004 (abstract). A prospective cohort study was conducted in 1985 to 1997 in western Norway to evaluate the impact of childhood ETS exposure on the risk of adult-onset asthma. The cohort included 2819 adults of an original cohort of 3786 persons aged 15 to 70 years who were evaluated 11 years earlier (74% completed both baseline and follow-up). ETS exposure was ascertained by self-report. Incident adult asthma was defined as self-reported asthma at follow-up among persons who did not report asthma at baseline. The attributable fraction was adjusted for the potential confounding effects of age, sex, educational attainment, atopy, active smoking, and occupational exposures. The adjusted attributable fraction due to maternal smoking, either in utero or in childhood, was 16.9% (95% CI 4.8 to 27.4%). The adjusted attributable fraction due to all childhood ETS, which included maternal smoking (pre- and post-natal) and other persons smoking, was 26.0% (95% CI 0.03 to 45.2%). The investigators evaluated ETS exposure from maternal smoking in more detail (Tomas Eagan, pers. comm., 9/15/04). Postnatal maternal smoking (without prenatal smoking) was associated with a greater risk of adult-onset asthma (OR 1.8; 95% CI 0.7 to 4.5) after controlling for confounders, although the confidence interval did not exclude no association. Prenatal maternal smoking, without postnatal smoking, was not common and was not statistically related to incident adult asthma (OR 1.8; 95% CI 0.2 to 15.9). The combination of maternal smoking pre- and post-natal was strongly associated with the development of adult-onset asthma (OR 3.5; 95% CI 1.8 to 6.8).

In sum, this prospective cohort study supports a link between childhood ETS exposure and the development of incident adult-onset asthma.

Jaakkola et al. (2003) examined the role of passive smoke exposure in the development of adult-onset asthma in a population-based case-control study of 239 asthma patients and 487 controls in Finland. The study population comprised clinically diagnosed new cases of asthma among 21-63-year-old adults between 1997 and 2000. Passive smoke exposure was assessed from self-administered questionnaires dealing with environmental factors in general (the Finnish Environment and Asthma Survey). Lifetime ETS exposure at home and at work, as well as ETS exposure during the preceding 12 months was determined. ETS exposure, in terms of the number of cigarettes per day and the duration of exposure, was determined for eight age periods (0-1, 1-6, 7-10, 11-15, 16-20, 21-30, 31-40, ≥ 40 years). Odds ratios were estimated by logistic regression analyses adjusted for gender, age, parental atopy or asthma, education (a proxy for SES), visible mold or mold odor, pets in the home, and occupational exposure to sensitizers, dusts or fumes (excluding ETS).

The incidence of adult-onset asthma was significantly associated with total ETS exposure (combined home and workplace) during the preceding 12 months (OR 1.97, 95% CI 1.19; 3.25) with evidence of an exposure response: OR 1.33 per 10 cigarettes per day (95% CI 1.02; 1.75). After controlling for exposure at home, any exposure to ETS in the workplace was also associated with an elevated risk of asthma (OR 2.16, 95% CI 1.26; 3.72) and an exposure response OR of 1.44 per 10 cigarettes per day (95% CI 1.03; 2.01). While there was significant risk associated with home exposure (OR 4.77, 95% CI 1.29; 17.7), the confidence limits were wide, reflecting the small number of cases, and there was no evidence of exposure response. These estimates were somewhat lower after adjustment for cumulative lifetime exposure (Table 6.52).

Analyzed as cumulative lifetime exposure, the risk of asthma was elevated, especially from workplace and combined exposures but many of the confidence intervals included no effect. There was some suggestion of an exposure response in the cumulative home and combined exposures but these trends did not achieve statistical significance.

The strengths of this study include the use of a questionnaire dealing with environmental factors in general rather than one that was ETS-specific. This may have reduced reporting bias among cases. In addition, the use of only clinically diagnosed, new cases of asthma avoided potential bias associated with self-diagnosis and possible ETS-related behavioral changes among previously diagnosed asthmatics. Another strength was the assessment of both recent and cumulative lifetime ETS exposures. However, recall bias may have affected the latter estimate and may, in part, explain the lack of an association with cumulative lifetime exposure. It is therefore difficult to determine the relative importance of recent versus cumulative exposures in the association of ETS with asthma. With respect to ETS in the home, the number of individuals reporting home exposure was small, severely limiting the assessment of this important source of exposure. Thus, concentrating on total and workplace exposures to ETS during the preceding 12 months, this study found a significant association between ETS and the onset of asthma in adults. The authors estimated that 49.2% of the asthma incidence among individuals exposed to ETS from all sources during the preceding year was attributable to the ETS exposure. This translated into an ETS-attributable fraction of 8% for the whole working age population.

Table 6.52 Risk of Adult-onset Asthma in Relation to ETS Exposure in the Preceding 12 Months and Cumulative Lifetime Exposure (from Jaakkola et al., 2003)

ETS during preceding 12 months			
Exposure	**Cases/Ctrls**	**OR (95% CI)[a]**	**OR (95% CI)[b]**
Workplace - any	34/41	2.16 (1.26; 3.72)	1.83 (1.05; 3.21)
1-9 cig/day	15/19	2.06 (0.97; 4.36)	1.85 (0.89; 3.98)
≥ 10 cig/day	12/12	2.90 (1.14; 7.34)	2.10 (0.81; 5.47)
Home - any	7/8	4.77 (1.29; 17.7)	3.83 (0.99; 14.8)
1-9 cig/day	4/3	3.93 (0.80; 19.4)	3.62 (0.71; 18.6)
≥ 10 cig/day	2/5	0.75 (0.13; 4.29)	0.56 (0.10; 3.30)
Combined - any	38/41	1.97 (1.19; 3.25)	1.66 (0.99; 2.76)
1-9 cig/day	17/22	2.13 (1.05; 4.30)	1.88 (0.92; 3.86)
≥ 10 cig/day	14/17	2.14 (0.95; 4.82)	1.56 (0.67; 3.61)
Cumulative lifetime ETS exposure			
Exposure	**Cases/Ctrls**	**OR (95% CI)[c]**	**OR (95% CI)[d]**
Workplace - cig-yrs			
1-49	32/70	1.17 (0.71; 1.93)	1.08 (0.65; 1.80)
50-99	15/17	2.35 (1.07; 5.14)	2.25 (1.03; 4.93)
100-149	7/18	1.28 (0.49; 3.31)	0.93 (0.34; 2.57)
≥ 150	22/27	2.21 (1.15; 4.27)	1.84 (0.93; 3.64)
Home - cig-yrs			
1-49	24/66	0.95 (0.55; 1.64)	0.99 (0.57; 1.71)
50-99	13/38	0.78 (0.39; 1.57)	0.81 (0.40; 1.62)
100-149	12/21	1.05 (0.48; 2.30)	1.09 (0.50; 2.40)
≥ 150	50/69	1.37 (0.87; 2.16)	1.40 (0.89; 2.20)
Combined - cig-yrs			
1-49	26/91	0.80 (0.48; 1.36)	0.79 (0.46; 1.34)
50-99	22/44	1.30 (0.71; 2.35)	1.28 (0.70; 2.34)
100-149	19/25	2.01 (1.02; 3.99)	1.76 (0.87; 3.55)
≥ 150	68/96	1.84 (1.21; 2.80)	1.71 (1.11; 2.64)

All ORS adjusted as described in the text with additional adjustment:
[a] for ETS exposure in other setting (work or home)
[b] for cumulative ETS exposure.
[c] for cumulative ETS exposure in other setting.
[d] for ETS exposure in past 12 months.

Iribarren et al., 2001. In a previous report, the authors examined cross-sectional data from 47,721 adult never-smoking Northern California Kaiser Permanente members who underwent multiphasic health check-ups between 1979 and 1985. Using a written questionnaire, current ETS exposure was ascertained for several locations: home, other small spaces (e.g., office or car), and large indoor spaces (e.g., restaurant). In each location, the survey assessed average duration of exposure. In both men and women, any ETS exposure was associated with a greater risk of self-reported physician-diagnosed asthma or hayfever (OR 1.22; 95% CI 1.11; 1.34 and

OR 1.14; 95% CI 1.06; 1.24, respectively), controlling for socioeconomic and demographic covariates. The risk estimates were similar for high level exposure (≥ 40 hours / week) compared to no exposure. For weekly exposure duration, there was evidence of an exposure-response relationship among women but not men.

Larsson et al., 2001. A population-based study of 8,008 adult never smokers from Sweden examined the impact of childhood ETS exposure on current self-reported physician-diagnosed asthma during adulthood. Adult asthma was more common among subjects who indicated childhood ETS exposure (7.6%) compared to unexposed persons (5.8%) (p=0.035). Current self-reported "breathing difficulties from cigarette smoke" were also more common among subjects who indicated a history of childhood ETS exposure. In further analysis, the authors stratified by family history of asthma. Although there was no clear impact of ETS among subjects without a family history of asthma, ETS exposure was associated with a greater risk of asthma among those with a positive family history (OR 1.82; 95% CI 1.28; 2.58). These results could be consistent with higher rates of smoking cessation by asthmatic parents, reducing exposure of their children with asthma.

Janson et al., 2001. The European Community Respiratory Health Survey investigators examined the respiratory health impacts of ETS exposure among 7,882 adult never smokers aged 20-48 years. Compared with no ETS exposure, any ETS exposure at home or work was not associated with a greater risk of self-reported current asthma (OR 1.15; 95% CI 0.84; 1.58). When each source of exposure was examined individually, workplace exposure was related to a higher risk of asthma (OR 1.90; 95% CI 1.25; 2.88). There was no apparent impact of home exposure (OR 1.14; 95% CI 0.68; 1.90). These apparently discrepant results could be explained by the method of ETS exposure measurement. Home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. Because residence with a smoker may not always reflect domestic ETS exposure (Eisner *et al.*, 2001), use of this exposure measure could attenuate the effect estimate for home ETS exposure.

The investigators also found a similar pattern of results for several asthma-like symptoms, including wheeze, nocturnal chest tightness, and dyspnea (nocturnal or exertional). In these

instances, workplace ETS exposure was related to a greater risk of respiratory symptoms, whereas home exposure had no apparent impact. An exposure-response relationship was noted for all respiratory symptoms, but not clearly for asthma. Furthermore, both home and workplace ETS exposure were associated with greater bronchial hyper-responsiveness (assessed by methacholine challenge). Because bronchial hyper-responsiveness is a cardinal feature of asthma, this result adds additional support to the observed link between ETS exposure and self-reported asthma.

Thorn et al., 2001. A Swedish population-based case-control study of adults 20-50 years old examined the impact of ETS exposure on the onset of asthma after age 16. The investigators ascertained home exposure only, during or previous to the year of asthma diagnosis (and at a randomly selected time for control subjects). In this study, ETS exposure was associated with a greater risk of adult-onset asthma (OR 2.4; 95% CI 1.4; 4.1). This increased risk was observed only among never smokers and not among current or ex-smokers. When the results were stratified by sex, the association was stronger for males (OR 4.8; 95% CI 2.0; 11.6) than females (OR 1.5; 95% CI 0.8; 3.1).

Kronqvist et al., 1999. Recent epidemiological studies have evaluated the impact of ETS exposure on new-onset adult asthma. A population-based cross-sectional study aimed to elucidate environmental risk factors for asthma and allergic rhinitis among Swedish dairy farmers. By postal questionnaire, asthma was defined as self-reported episodic respiratory symptoms, such as wheezing and dyspnea. ETS exposure was assessed for the current period (home and work) and during childhood. In this study, no measure of ETS exposure, past or present, was associated with the risk of asthma (OR or RR were not reported) (Table 6.51).

Hu et al. (1997b) evaluated a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. At baseline, ETS exposure status was determined by parental reports of personal smoking. During young adulthood (seven years later), self-reported physician diagnosed asthma was ascertained by written questionnaire. Exposure to parental ETS at baseline was associated with an increased risk of subsequent asthma. Compared with no maternal smoking or light smoking at baseline ($\leq$ one-half pack per day), heavier maternal smoking was associated with an increased risk of self-reported asthma in

young adulthood (OR 1.8; 95% CI 1.1; 3.0). Similarly, heavy paternal smoking was related to a greater risk of asthma (OR 1.6; 95% CI 1.1; 2.4). In addition, they observed an exposure-response relationship between number of parents smoking at baseline and the risk of asthma seven years later.

Flodin et al., 1995. A population-based case-control study from semi-rural Sweden evaluated ETS exposure as a risk factor for adult onset asthma ($\geq$ age 20 years). During a 9 month period, cases were identified from all persons filling a prescription for beta-agonist medications in two communities. The diagnosis of asthma was confirmed by a pulmonary specialist. Controls were randomly selected from a general population register and matched to cases by age (of asthma diagnosis), gender, and community. ETS exposure at both home and work was assessed by written questionnaire, which was defined as exposure for at least 3 years prior to the age at asthma diagnosis (or comparable age for controls). Workplace ETS exposure was associated with an increased risk of asthma (OR 1.5; 95% CI 0.8; 2.5), but the confidence interval did not exclude no relationship. Exposure to ETS at home was not associated with a greater risk of asthma (OR 0.9; 95% CI 0.5; 1.5).

Greer et al., 1993; McDonnell et al., 1999. A longitudinal cohort study of 3,914 adult non-smoking Seventh-Day Adventists living in California evaluated the relationship between ETS exposure and the incidence of self-reported physician diagnosed asthma during a 15-year period. The investigators reported the 10-year (Greer *et al.*, 1993) and 15-year cohort follow-up (McDonnell *et al.*, 1999). As reported in the 1997 Cal/EPA report, duration of working with a smoker was associated with an increased risk of developing asthma (OR 1.5 per 10-year increment; 95% CI 1.2; 1.8). Since the 1997 Cal/EPA report, longer-term follow-up of the cohort has been reported. At 15-year follow-up, duration of working with a smoker was associated with an increased risk of incident asthma for women only (OR 1.21; 95% CI 1.04; 1.39). In both analyses, there was no reported relationship between duration of residence with a smoker and risk of asthma.

There is no "gold standard" for defining asthma in epidemiological research. Although self-reported asthma is commonly used in survey research, this definition may not detect all persons with asthma (McWhorter *et al.*, 1989; Toren *et al.*, 1993). Respondents' reports of respiratory

symptoms, especially wheezing, may have a greater sensitivity for identifying adults with asthma (Toren *et al.*, 1993). Wheezing, in particular, correlates with the criterion of bronchial hyper-responsiveness (Burney *et al.*, 1989).

The previous 1997 Cal/EPA report reviewed studies that support the relationship between ETS exposure and wheezing among adults (Comstock *et al.*, 1981; Jaakkola *et al.*, 1996; Kauffmann *et al.*, 1989; Leuenberger *et al.*, 1994; Ng *et al.*, 1993). Two recent studies further support the adverse impact of ETS exposure on the risk of wheezing among adults (Table 6.53).

Table 6.53 ETS and New Onset of Wheezing Among Adolescents and Adults

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Withers *et al* 1998 U.K.	Cohort: 6-8 yr followed 8 yrs n = 2,289	Parent report Maternal ETS Paternal ETS	Wheeze 1.48 (1.17; 1.88) Asthma 1.50 (1.14; 1.98) New onset wheeze 1.55 (1.03; 2.32)	ETS associated w/current and new wheeze. Maternal ETS w/current asthma; Paternal w/new wheeze.
Strachan *et al* 1996 U.K.	Cohort: 0-adult Adult wheeze n = 18,559	Maternal ETS Child at 16 yr Prenatal + 16	New onset wheeze at 33 1.19 (0.86; 1.65) 1.40 (1.08; 1.82)	Combined pre- and post-natal maternal ETS raise wheeze risk at 33 yrs.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity

Withers et al., 1998. A population-based longitudinal cohort study from the U.K. followed children aged 6-8 years into adolescence (age 14-16 years) to examine factors associated with the development of respiratory symptoms. In adolescence, ETS exposure was cross-sectionally associated with current wheeze (OR 1.48; 95% CI 1.17; 1.88). Maternal smoking was related to a greater risk of parent-reported physician-diagnosed asthma (OR 1.50; 95% CI 1.14; 1.98). There was no apparent impact of paternal smoking on current asthma. Among previously asymptomatic persons, paternal smoking was associated with new-onset wheeze during prospective follow-up (OR 1.55; 95% CI 1.03; 2.32). Maternal smoking, however, was not associated with new-onset wheeze. New-onset asthma was not examined.

Strachan et al., 1996. Another population-based U.K. cohort study followed 18,559 children born during a single week in March, 1958 through age 33 (31% complete follow-up). The study examined the association between household ETS exposure and the future incidence of wheezing. At both age 7 and 33 years, maternal smoking during pregnancy was associated with

an increased risk of incident wheezing illness (OR 1.72; 95% CI 1.11; 2.67 and OR 1.71; 95% CI 0.97; 3.0, respectively). At age 33, maternal smoking at subject age 16 was associated with an increased incidence of wheezing (OR 1.19; 95% CI 0.86; 1.65), although the 95% C.I. includes no effect. ETS exposure both during pregnancy and age 16 was related to a greater risk of incident wheezing (OR 1.4; 95% CI 1.08; 1.82). This study is limited by the low follow-up at age 33, which could have biased the results if ETS exposure was related to the probability of study participation.

In the 2004 Surgeon General's report on the health consequences of smoking (DHHS, 2004), the role of active smoking in the etiology of adult-onset asthma was examined. From a survey of 14 longitudinal and cross-sectional studies published between 1988 and 2001, the report concluded that "the evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults." For most of the studies cited, the risks for asthma induction were elevated but in several, the confidence intervals included no effect. The report mentioned that various methodological limitations, biases, differences in study designs, and varying definitions of asthma likely contributed to the apparent inconsistencies in the findings. This update presents several newer studies (Eagan *et al*., 2004; Jaakkola *et al*., 2003; Iribarren *et al.*, 2001; Larsson *et al*, 2001) not included in the Surgeon General's report that better address the limitations noted above, and find a significant association between ETS exposure and adult-onset asthma.

6.5.2.2. Conclusions – Asthma Induction in Adolescents and Adults

A number of the studies in this section included adolescents as adults, thus in the discussion that follows, the term "adult" applies to the combined group. In interpreting these epidemiological studies, a critical issue is whether the observed association between ETS exposure and adult asthma could be explained by confounding factors. ETS exposure has been associated with younger age, female gender, non-white race, lower education, lower income, blue-collar occupation, and personal cigarette smoking (Hole *et al.*, 1989; Iribarren *et al.*, 2001; Mannino *et al.*, 1997; Sippel *et al.*, 1999). Many of these factors have also been associated with an increased prevalence of asthma and asthma-related morbidity (Mannino *et al.*, 1997). As a result, a given risk estimate for ETS exposure could be potentially explained by confounding. Although these studies had variable control for confounding factors, most investigators examined at least some

potential confounders. Overall, the observed relationship between ETS exposure and asthma is probably not explained by confounding.

Measurement of ETS exposure by self-report is potentially subject to bias, which limits interpretation of all the studies reviewed. The impact of exposure misclassification may be particularly problematic in cross-sectional studies. For example, adults with asthma might be more likely to remember and report ETS exposure, whereas asymptomatic persons might underreport ETS exposure. This bias would inflate the estimated risk associated with ETS exposure. In all studies examined, systematic misclassification of ETS exposure cannot be excluded. The prospective data, however, should be less affected by this potential bias. Moreover, studies that employed direct markers of ETS exposure, such as cotinine or personal nicotine exposure, would not be affected by this reporting bias.

Examination of the Bradford Hill (1971) criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were observed for total daily duration of ETS exposure (Leuenberger *et al.*, 1994), number of smokers in the environment (Hu *et al.*, 1997a; Leuenberger *et al.*, 1994), duration of exposure to smokers (Iribarren *et al.*, 2001; Janson *et al.*, 2001; Kunzli *et al.*, 2000; Leuenberger *et al.*, 1994), duration of working with a smoker (Greer *et al.*, 1993; McDonnell *et al.*, 1999), measured nicotine levels (Eisner *et al.*, 2001), and an ETS exposure index that incorporates both intensity and duration of exposure (Jaakkola *et al.*, 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larson 2001), a defined period prior to the diagnosis of asthma (Flodin *et al.,* 1995, Thorn *et al.,* 2001, Hu *et al.,*1997b, Greer *et al.,* 1993, McDonnell *et al.,* 1999), or a defined period prior the the development of asthma-like symptoms (Withers *et al.,* 1998,

Strachan *et al.,* 1996). In these studies, exposure to ETS clearly predated the development of asthma.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed the association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a deleterious causal effect of ETS exposure on adult asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation.(Cal/EPA, 1997) Studies linking ETS exposure with a decrement in pulmonary function support the biologic plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function (Hole *et al.* 1989; Comstock *et al.* 1981; Ng *et al.* 1993; Masi *et al.* 1988; O'Connor *et al.* 1987; Xu and Li 1995; Schilling *et al.* 1977; Kauffmann *et al.* 1989; Brunekreef *et al.* 1985; Abbey *et al.* 1998; Carey *et al.* 1999; Jaakkola *et al.* 1995; Eisner *et al.* 1998; Eisner 2002).

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association.

A key issue is distinguishing the development of incident adult-onset asthma, as opposed to exacerbation of previously established disease. Several studies directly support the impact of ETS exposure on incident adult asthma (Thorn *et al.,* 2001; Hu *et al.,* 1997b, Greer *et al.,* 1993; McDonnell *et al.,* 1999; and Jaakkola *et al.,* 2003). Other studies have prospectively examined

the relation between ETS exposure and incident wheezing (Withers *et al.,* 1998, Strachan *et al.,* 1996). The population-based study by Jaakkola and colleagues provides the strongest evidence to date that links ETS exposure to incident adult asthma. The investigators used a systematic surveillance system to identify newly diagnosed adult asthma cases in a region of Finland and to exclude pre-existing asthma cases. ETS exposure assessment ascertained exposure history during the past 12 months and the entire lifetime. Taken together, these studies indicate that ETS exposure is associated with the subsequent development of incident adult asthma.

In sum, studies of ETS and adult-onset asthma have controlled for bias and confounding. They have demonstrated temporality, exposure-response relationship, consistency, coherence, and biologic plausibility, supporting a causal relationship.

The long-term health consequences of ETS exposure have been established over the past two decades. Consistent epidemiological evidence links ETS exposure with serious chronic health effects, including lung cancer and cardiovascular disease (Cal EPA, 1997; Hackshaw *et al.*, 1997; Kawachi *et al.*, 1997). As discussed in depth in each of the previous sections in the present review, the evidence is consistent with a causal relationship between ETS exposure and new-onset asthma and asthma exacerbations in young and older children. In addition, the new studies also provide evidence for a causal relationship between ETS exposure and new-onset asthma and asthma exacerbation among adults. Despite the growing knowledge of ETS-related health effects, smoking is still permitted in many public locations and workplaces (Emmons *et al.*, 1996; Gerlach *et al.*, 1997). Because asthma is a visible condition among the general public, the evidence linking ETS exposure with adverse asthma health outcomes should provide policymakers with additional impetus for regulating public smoking and creating smoke-free public environments.

6.6. Susceptible Populations

From the body of research reviewed here, it is evident that there are populations with enhanced susceptibility to the deleterious effects of ETS. These groups are defined by age, predisposing conditions and previous exposures. ETS exposure puts neonates and infants at greater risk for the onset and exacerbation of asthma (Stoddard and Miller, 1995; Wennergren *et al.*, 1997; Mannino *et al.*, 2001). Young children are especially impacted by asthma; they have the highest

hospitalization rates compared to older children and adults, probably at least in part due to their smaller airways resulting in more serious obstruction. Compared to older children and adults, ETS exposure puts neonates and infants at greater risk for respiratory tract infections (Li *et al.*, 1999), otitis media, and symptoms of respiratory illness (Gergen *et al.*, 1998). Individuals with preexisting allergies or atopy tend to be more severely affected by ETS exposure (Jedrychowski and Flak, 1997; Lindfors *et al.*, 1995; Hajnal *et al.*, 1999). As reviewed above, both children and adults with current asthma are especially susceptible to ETS.

In addition to these conditions, an individual's susceptibility to ETS exposure is enhanced by prior exposure to tobacco products early in development. Children exposed to tobacco smoke constituents *in utero* through either active or passive maternal smoking during pregnancy are even more affected by subsequent ETS exposure with more pronounced respiratory symptoms (Hajnal *et al.*, 1999), higher respiratory infection rates (Jedrychowski and Flak, 1997; Strachan and Cook, 1997; Gilliland *et al.*, 2001), and decreased pulmonary function (Mannino *et al.*, 2001; Li *et al.*, 2000; Rizzi *et al.*, 2004; Svanes *et al.*, 2004). Thus maternal exposure to tobacco smoke during pregnancy helps create a population at greater risk for the subsequent development of ETS-associated diseases.

6.6.1. ETS and Cystic Fibrosis

The 1997 document (CalEPA 1997) summarized the extent and magnitude of the effects of ETS on individuals with cystic fibrosis (CF) as uncertain. While the evidence for an effect of ETS on CF-related hospitalizations was reportedly compelling, it was less conclusive regarding effects on pulmonary function or disease severity. The two additional studies described below do little to change that assessment. While the study by Beydon *et al*. (2002) suggests a negative effect of ETS exposure in CF, the study by Smyth *et al.* (2001) finds no ETS effect on two measures of lung function in children with CF.

Beydon et al. (2002) conducted pulmonary function tests in 39 preschool children with, and 79 without CF. All children received a physical examination during which height, weight and history of ETS exposure were recorded. For CF children additional information collected included CF transmembrane conductance regulator gene mutations, circumstances of diagnosis, pancreatic insufficiency, CF-related respiratory symptoms, history of respiratory infection,

intravenous antibiotic use, and anti-asthma treatments. The pulmonary function tests included measures of functional residual capacity (FRC) and expiratory interrupter resistance ($Rint_{exp}$) for which both absolute values and Z-scores were presented. Children with CF had significantly higher $Rint_{exp}$ values and $Rint_{exp}$ Z-scores than did healthy children ($p<0.0001$). Increases in $Rint_{exp}$ or its Z-score reflect occlusion of the lower airways. Of the 39 children with CF, 8 had ETS exposure and higher baseline $Rint_{exp}$ Z-scores than the other 31 (median $Rint_{exp}$ Z-scores 2.4 (0.8-3.5) versus 0.6 (0-1.7); $p < 0.03$). An analysis of the effects of genotype and passive smoking among CF children indicated that passive smoking was the main risk factor for having a $Rint_{exp}$ Z-score greater than 2 (OR 9.5, $p < 0.03$). The significant elevation of the $Rint_{exp}$ Z-score in CF children with ETS exposure was not observed among control children with, versus without, ETS exposure. This study was small and not specifically designed to examine the effects of passive smoking. Thus information on the degree of ETS exposure is limited. Nevertheless, ETS exposure was associated with significant airway obstruction in preschool children with CF.

Smyth et al. (2001) investigated trends in ETS exposure in children with cystic fibrosis (CF) over a five-year period. Smoke exposure was assessed both by questionnaire and by measures of urinary and salivary cotinine. Cross-sectional data were obtained on 52 children with CF in 1993 (ages 5-16 years). Similar cross-sectional data were collected on 56 children in 1998 (ages 5-18 years), 34 of whom were included in the 1993 group. Lung function tests were performed on both occasions to measure FEV_1 and FVC. Family smoking behavior was not different between the groups examined in 1993 and 1998. Among the 34 children tested on both occasions, there was no significant change in the log urinary cotinine values (5.03 ng/ml vs 4.76 ng/ml, $p = 0.4$). However, these values were apparently not corrected for volume. Measures of FEV1 and FVC declined in children from both smoking and non-smoking households and there was no significant difference in the decline between the two.

In healthy children, FEV1 and FVC normally increase as the child grows while ETS exposure decreases this expected increase (Tager *et al*., 1983). By contrast, children with CF typically show a decrease in lung function with age. In this study, children with CF showed a decrease in lung function of approximately the same amount (10-11%) whether or not they were exposed to ETS. Thus ETS exposure was not seen to exacerbate the CF-associated decrease in lung

function. The authors observed that it is not known to what extent parents of children with mild symptoms were less likely to modify their smoking behaviors, and hence the child's ETS exposure, compared to parents of severely affected children. Such an effect could mitigate any negative effects of ETS exposure.

6.7. Chapter Summary and Conclusions

6.7.1. Effects of ETS on Children

ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract, especially in children. The number and severity of these effects appear to be inversely related to the age at which tobacco exposure commences, with the greatest susceptibility associated with exposure starting *in utero*. This age-related sensitivity to ETS undoubtedly reflects not only the developmental susceptibility of the very young but also changing patterns of exposure as growing children spend less time in close proximity to sources of ETS.

In the context of lung development, data presented in the previous document were deemed to be suggestive of a causal association. However, based on the studies in this update, OEHHA finds that the data conclusively demonstrate a causal association between ETS exposure and decrements in measures of lung development. In all the reviewed studies using forced expiratory volume (FEV) as a measure of lung function, significant decrements were observed in children exposed to ETS. Two studies measured cotinine in children and found that decrements in the spirometric measures were associated with elevated cotinine indicating recent exposure to tobacco smoke.

As seen in this review, ETS continues to be causally associated with the onset and exacerbation of asthma, and increased frequency of respiratory infections and disease symptoms in children. With current asthma, ETS exposure worsened symptoms, increased the number of symptomatic days and increased usage of healthcare services. That recent ETS exposure contributed to these endpoints was indicated by the positive association of cotinine with asthma symptoms in children.

The case for the involvement of ETS in new-onset asthma has been most compellingly made for children, especially young children and those whose mothers smoked during pregnancy. Of the

37 studies included in this review, nearly all showed a positive correlation with postnatal ETS (OR >1.0 or $p<0.05$). In the OEHHA meta-analysis, an abstract of which is presented here, an analysis based on 29 studies that controlled for the child's history of atopy and personal smoking, and in which all ages were combined, gave a pooled OR for new-onset asthma of 1.32 (95% CI, 1.24; 1.41). Studies allowing stratification by age indicated that the earlier a child is exposed to ETS, the greater the risk for asthma induction. In another sub-analysis in the OEHHA meta-analysis, postnatal-only exposure resulted in elevated asthma risk in seven of eight studies, and that risk was statistically significant in three of the studies.

In children, ETS is also associated with otitis media. In California, ETS-related otitis media cases are estimated to result in 30,820 to 78,877 office visits per year among children less than three years of age.

The studies in children reviewed here all indicate that smoke exposure increases the risk of respiratory illness by 26 to 113%. This effect was dose-related and especially pronounced in young children and children with atopy.

6.7.2. Effects of ETS on Adults

For two respiratory outcomes in adults, asthma induction and asthma exacerbation, the research published since the 1997 Cal/EPA document supports a change in the estimation of the causal association from suggestive to conclusive. In adults, diagnosed asthma or wheeze was significantly associated with ETS exposure in 8 of 10 studies, especially where exposure started *in utero*, in childhood, and/or where there was a family history of asthma. In adult asthmatics, nicotine exposure (as monitored by personal badge) was linearly correlated with respiratory symptoms. Collectively the studies of ETS and adult-onset asthma satisfy the Bradford Hill criteria for a causal association in that they have demonstrated temporality, exposure-response relationship, consistency, coherence, and biologic plausibility.

While lung function effects are less pronounced in adults than in children, ETS exposure appears to play a role in the genesis of chronic lower respiratory tract symptoms in otherwise healthy individuals and produces small, but measurable, decrements in pulmonary function. In adults, exposure to ETS at home and/or work was less associated with the onset of respiratory illness but rather with the aggravation of the symptoms and severity of existing bronchitis, sinusitis and

emphysema. Among adult nonsmokers exposed to ETS, eye, nose and throat irritation, as well as odor annoyance, are the most commonly reported health complaints. These complaints occur at levels near or overlapping the odor threshold for ETS, making their prevention technically difficult in smoking-permitted buildings.

This section thus finds ETS exposure in adults to be causally associated with asthma induction and exacerbation, and sensory irritation. An association with the worsening of respiratory symptoms is also strongly indicated.

6.8. References

Abbey DE, Burchette RJ, Knutsen SF, McDonnell WF, Lebowitz MD, Enright PL (1998). Long-term particulate and other air pollutants and lung function in nonsmokers. Am J Respir Crit Care Med 158(1):289-98.

Abramson MJ, Kutin JJ, Rosier MJ, Bowes G (1995). Morbidity, medication and trigger factors in a community sample of adults with asthma. Med J Aust 162(2):78-81.

Abulhosn RS, Morray BH, Llewellyn CE, Redding GJ (1997). Passive smoke exposure impairs recovery after hospitalization for acute asthma. Arch Pediatr Adolesc Med 151(2):135-9.

Agabiti N, Mallone S, Forastiere F, Corbo GM, Ferro S, Renzoni E, Sestini P, Rusconi F, Ciccone G, Viegi G, Chellini E, Piffer S.. (1999). The impact of parental smoking on asthma and wheezing. SIDRIA Collaborative Group. Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente. Epidemiology 10(6):692-8.

Al-Dawood K (2001). Parental smoking and the risk of respiratory symptoms among schoolboys in Al-Khobar City, Saudi Arabia. J Asthma 38 (2):149-54.

Avunduk AM, Avunduk MC, Evirgen O, Yardimci S, Tastan H, Guven C, Cetinkaya K. (1997). Histopathological and ultrastructural examination of the rat conjunctiva after exposure to tobacco smoke. Ophthalmologica 211(5):296-300.

Azizi BH, Henry RL (1991). The effects of indoor environmental factors on respiratory illness in primary school children in Kuala Lumpur. Int J Epidemiol 20(1):144-50.

Azizi BH, Zulkifli HI, Kasim S (1995). Indoor air pollution and asthma in hospitalized children in a tropical environment. J Asthma 32(6):413-8.

Bascom R, Kesavanathan J, Fitzgerald TK, Cheng KH, Swift DL (1995). Sidestream tobacco smoke exposure acutely alters human nasal mucociliary clearance. Environ Health Perspect 103(11):1026-30.

Bascom R, Kesavanathan J, Permutt T, Fitzgerald TK, Sauder L, Swift DL (1996). Tobacco smoke upper respiratory response relationships in healthy nonsmokers. Fundam Appl Toxicol 29(1):86-93.

Bascom R, Kulle T, Kagey-Sobotka A, Proud D (1991). Upper respiratory tract environmental tobacco smoke sensitivity. Am Rev Respir Dis 143(6):1304-11.

Bearer C, Emerson RK, O'Riordan MA, Roitman E, Shackleton C (1997). Maternal tobacco smoke exposure and persistent pulmonary hypertension of the newborn. Environ Health Perspect 105(2):202-6.

Beckett WS, Belanger K, Gent JF, Holford TR, Leaderer BP (1996). Asthma among Puerto Rican Hispanics: a multi-ethnic comparison study of risk factors. Am J Respir Crit Care Med 154(4 Pt 1):894-9.

Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4):1088-101.

Bek K, Tomac N, Delibas A, Tuna F, Tezic HT, Sungur M (1999). The effect of passive smoking on pulmonary function during childhood. Postgrad Med J 75(884):339-41.

Berglund DJ, Abbey DE, Lebowitz MD, Knutsen SF, McDonnell WF (1999). Respiratory symptoms and pulmonary function in an elderly nonsmoking population. Chest 115(1):49-59.

Beydon, N.; Amsallem, F.; Bellet, M.; Boule, M.; Chaussain, M.; Denjean, A.; Matran, R.; Pin, I.; Alberti, C., and Gaultier, C. (2002). Pulmonary function tests in preschool children with cystic fibrosis. Am J Respir Crit Care Med. 166(8):1099-104.

Blanc PD, Ellbjar S, Janson C, Norback D, Norrman E, Plaschke P, Toren K. (1999). Asthma-related work disability in Sweden. The impact of workplace exposures. Am J Respir Crit Care Med 160(6):2028-33.

Bono R, Nebiolo F, Bugiani M, Meineri V, Scursatone E, Piccioni P, Caria E, Gilli G, Arossa W. (1998). Effects of tobacco smoke exposure on lung growth in adolescents. J Expo Anal Environ Epidemiol 8(3):335-45.

Borchers MT, Carty MP, Leikauf GD (1999). Regulation of human airway mucins by acrolein and inflammatory mediators. Am J Physiol 276(4 Pt 1):L549-55.

Bradford Hill A (1971). Statistical Evidence and Inference. In Principles of Medical Statistics. Oxford University Press, Oxford, UK /New York, NY. pp. 309-323.

Brunekreef B, Fischer P, Remijn B, van der Lende R, Schouten J, Quanjer P (1985). Indoor air pollution and its effect on pulmonary function of adult non-smoking women: III. Passive smoking and pulmonary function. Int J Epidemiol 14(2):227-30.

Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, Poisson N, Heeren A, Britton JR, Jones T. (1989). Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. Eur Respir J 2(10):940-5.

Burr ML, Miskelly FG, Butland BK, Merrett TG, Vaughan-Williams E (1989). Environmental factors and symptoms in infants at high risk of allergy. J Epidemiol Community Health 43(2):125-32.

Cal EPA (1997). Health effects of exposure to environmental tobacco smoke. Sacramento, CA: California Environmental Protection Agency.

CA DHS (2001). The California tobacco control program: a decade of progress, results from the California Tobacco Survey, 1990-1999. Sacramento, CA: California Department of Health Services, Tobacco Control Section.

Carey IM, Cook DG, Strachan DP (1999). The effects of environmental tobacco smoke exposure on lung function in a longitudinal study of British adults. Epidemiology 10(3):319-26.

CDC (1997). State-specific prevalence of cigarette smoking among adults, and children's and adolescents' exposure to environmental tobacco smoke – United States, 1996. MMWR 46(44): 1038-1043.

CDC (2002). Surveillance for asthma – United States, 1980-1999. MMWR 51 (SS-1).

Chen Y (1989). Synergistic effect of passive smoking and artificial feeding on hospitalization for respiratory illness in early childhood. Chest 95(5):1004-7.

Chen Y, Li WX (1986). The effect of passive smoking on children's pulmonary function in Shanghai. Am J Public Health 76(5):515-8.

Chen Y, Li WX, Yu SZ, Qian WH (1988). Chang-Ning epidemiological study of children's health: I: Passive smoking and children's respiratory diseases. Int J Epidemiol 17(2):348-55.

Chen Y (1994). Environmental tobacco smoke, low birth weight, and hospitalization for respiratory disease. Am J Respir Crit Care Med 150(1):54-8.

Chen Y, Rennie DC, Dosman JA (1996). Influence of environmental tobacco smoke on asthma in nonallergic and allergic children. Epidemiology 7(5):536-9.

Chilmonczyk BA, Salmun LM, Megathlin KN, Neveux LM, Palomaki GE, Knight GJ, Pulkkinen A J, Haddow JE.. (1993). Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. N Engl J Med 328(23):1665-9.

CHIS (2001). California Health Information Survey, 2001. Data available at : http://chis.ucla.edu.

Coggins CR, Lovejoy HM, McGuirt WF, Sagartz JW, Hayes AW, Ayres PH (1997). Relevant exposure to environmental tobacco smoke surrogate does not produce or modify secretory otitis media in the rat. Toxicol Pathol 25(4):395-7.

Comstock GW, Meyer MB, Helsing KJ, Tockman MS (1981). Respiratory effects on household exposures to tobacco smoke and gas cooking. Am Rev Respir Dis 124(2):143-8.

Cook DG, Strachan DP, Carey IM (1998). Health effects of passive smoking. 9. Parental smoking and spirometric indices in children. Thorax 53(10):884-93.

Crombie IK, Wright A, Irvine L, Clark RA, Slane PW (2001). Does passive smoking increase the frequency of health service contacts in children with asthma? Thorax 56(1):9-12.

Cunningham J, O'Connor GT, Dockery DW, Speizer FE (1996). Environmental tobacco smoke, wheezing, and asthma in children in 24 communities. Am J Respir Crit Care Med 153(1):218-24.

Cunningham J,Dockery DW, Speizer FE. (1994). Maternal smoking during pregnancy as a predictor of lung function in children. Am J Epidemiol. 139(12):1139-52.

Cunningham J, Dockery DW, Gold DR, Speizer FE. (1995). Racial differences in the association between maternal smoking during pregnancy and lung function in children. Am J Respir Crit Care Med.152(2):565-9.

Dales RE, Kerr PE, Schweitzer I, Reesor K, Gougeon L, Dickinson G (1992). Asthma management preceding an emergency department visit. Arch Intern Med 152(10):2041-4.

Dalton P, Wysocki CJ, Brody MJ, Lawley HJ (1997). The influence of cognitive bias on the perceived odor, irritation and health symptoms from chemical exposure. Int Arch Occup Environ Health 69(6):407-17.

Dayal HH, Khuder S, Sharrar R, Trieff N (1994). Passive smoking in obstructive respiratory disease in an industrialized urban population. Environ Res 65(2):161-71.

Dubus JC, Oddoze C, Badier M, Guillot C, Bruguerolle B (1998). Possible interaction between exposure to environmental tobacco smoke and therapy in children with asthma. Clin Sci (Lond) 95(2):143-9.

Eagan T, Duelien T, Eide G, Gulsvik A, Bakke P. (2004). The adjusted attributable fraction of adult asthma and respiratory symptoms due to environmental tobacco smoke in childhood. Eur Respir J 24 (Sup 28) ; 22s.

Ehrlich R, Jordaan E, Du Toit D, Potter P, Volmink J, Zwarenstein M, Weinberg E. (2001). Household smoking and bronchial hyperresponsiveness in children with asthma. J Asthma 38(3):239-51.

Ehrlich RI, Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA, Weinberg E.. (1996). Risk factors for childhood asthma and wheezing. Importance of maternal and household smoking. Am J Respir Crit Care Med 154(3 Pt 1):681-8.

Eisner MD (2002). Environmental tobacco smoke exposure and pulmonary function among adults in NHANES III: impact on the general population and adults with current asthma.

Eisner MD, Katz PP, Yelin EH, Hammond SK, Blanc PD (2001). Measurement of environmental tobacco smoke exposure among adults with asthma. Environ Health Perspect 109(8):809-14.

Eisner MD, Smith AK, Blanc PD (1998). Bartenders' respiratory health after establishment of smoke-free bars and taverns. JAMA 280(22):1909-14.

Ekwo EE, Weinberger MM, Lachenbruch PA, Huntley WH (1983). Relationship of parental smoking and gas cooking to respiratory disease in children. Chest 84(6):662-8.

Elliot J, Vullermin P, Robinson P. (1998). Maternal cigarette smoking is associated with increased inner airway wall thickness in children who die from sudden infant death syndrome. Am J Respir Crit Care Med.158(3):802-6.

Emmons KM, Marcus BH, Abrams DB, Marshall R, Novotny TE, Kane ME, Etzel RA. (1996). Use of a 24-hour recall diary to assess exposure to environmental tobacco smoke. Arch Environ Health 51(2):146-9.

Etzel RA, Pattishall EN, Haley NJ, Fletcher RH, Henderson FW (1992). Passive smoking and middle ear effusion among children in day care. Pediatrics 90(2 Pt 1):228-32.

Farber HJ, Wattigney W, Berenson G (1997). Trends in asthma prevalence: the Bogalusa Heart Study. Ann Allergy Asthma Immunol 78(3):265-9.

Fergusson DM, Horwood LJ (1985). Parental smoking and respiratory illness during early childhood: a six-year longitudinal study. Pediatr Pulmonol 1(2):99-106.

Ferris BG Jr, Ware JH, Berkey CS, Dockery DW, Spiro A 3rd, Speizer FE (1985). Effects of passive smoking on health of children. Environ Health Perspect 62:289-95.

Flodin U, Jonsson P, Ziegler J, Axelson O (1995). An epidemiologic study of bronchial asthma and smoking. Epidemiology 6(5):503-5.

Forastiere F, Corbo GM, Michelozzi P, Pistelli R, Agabiti N, Brancato G, Ciappi G, Perucci CA (1992). Effects of environment and passive smoking on the respiratory health of children. Int J Epidemiol 21(1):66-73.

Gardner G, Frank AL, Taber LH (1984). Effects of social and family factors on viral respiratory infection and illness in the first year of life. J Epidemiol Community Health 38(1):42-8.

Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. (2004). The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 351(11):1057-67.

Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD (1998). The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. Pediatrics 101(2):E8.

Gerlach KK, Shopland DR, Hartman AM, Gibson JT, Pechacek TF (1997). Workplace smoking policies in the United States: results from a national survey of more than 100,000 workers. Tob Control 6(3):199-206.

Gilliland FD, Berhane K, Islam T, Wenten M, Rappaport E, Avol E, Gauderman WJ, McConnell R, Peters JM. (2003). Environmental tobacco smoke and absenteeism related to respiratory illness in schoolchildren. Am J Epidemiol 157(10):861-9.

Gilliland FD, Li YF, Peters JM (2001). Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. Am J Respir Crit Care Med 163(2):429-36.

Gilpin E , Emery S , Farkas A , Distefan J , White M , Pierce J (2001). The California Tobacco Control Program: a decade of progress, results from the California tobacco survey, 1990-1999. California Department of Health Services.

Greer JR, Abbey DE, Burchette RJ (1993). Asthma related to occupational and ambient air pollutants in nonsmokers. J Occup Med 35(9):909-15.

Gryczynska D , Kobos J, Zakrzewska A (1999). Relationship between passive smoking, recurrent respiratory tract infections and otitis media in children. Int J Pediatr Otorhinolaryngol 49 Suppl 1:S275-8.

Gupta D, Aggarwal AN, Kumar R, Jindal SK (2001). Prevalence of bronchial asthma and association with environmental tobacco smoke exposure in adolescent school children in Chandigarh, north India. J Asthma 38(6):501-7.

Gurkan F, Kiral A, Dagli E, Karakoc F (2000). The effect of passive smoking on the development of respiratory syncytial virus bronchiolitis. Eur J Epidemiol 16(5):465-8.

Hackshaw AK, Law MR, Wald NJ (1997). The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 315(7114):980-8.

Hajnal BL, Braun-Fahrlander C, Grize L, Gassner M, Varonier HS, Vuille JC, Wuthrich B, Sennhauser FH. (1999). Effect of environmental tobacco smoke exposure on respiratory symptoms in children. SCARPOL Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen. Schweiz Med Wochenschr 129(19):723-30.

Hakansson A, Carlsson B (1992). Maternal cigarette smoking, breast-feeding, and respiratory tract infections in infancy. A population-based cohort study. Scand J Prim Health Care 10(1):60-5.

Halken S, Host A, Husby S, Hansen LG, Osterballe O, Nyboe J (1991). Recurrent wheezing in relation to environmental risk factors in infancy. A prospective study of 276 infants. Allergy 46(7):507-14.

Hall CB, Hall WJ, Gala CL, MaGill FB, Leddy JP (1984). Long-term prospective study in children after respiratory syncytial virus infection. J Pediatr 105(3):358-64.

Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, Weiss ST, Speizer FE. (1992). The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 145(5):1129-35.

Hayes EB, Hurwitz ES, Schonberger LB, Anderson LJ (1989). Respiratory syncytial virus outbreak on American Samoa. Evaluation of risk factors. Am J Dis Child 143(3):316-21.

Hole DJ, Gillis CR, Chopra C, Hawthorne VM (1989). Passive smoking and cardiorespiratory health in a general population in the west of Scotland. BMJ 299(6696):423-7.

Hu FB, Persky V, Flay BR, Zelli A, Cooksey J, Richardson J (1997a). Prevalence of asthma and wheezing in public schoolchildren: association with maternal smoking during pregnancy. Ann Allergy Asthma Immunol 79(1):80-4.

Hu FB, Persky V, Flay BR, Richardson J (1997b). An epidemiological study of asthma prevalence and related factors among young adults. J Asthma 34(1):67-76.

Ilicali OC, Keles N, De er K, Sa un OF, Guldiken Y (2001). Evaluation of the effect of passive smoking on otitis media in children by an objective method: urinary cotinine analysis. Laryngoscope 111(1):163-7.

Infante-Rivard C (1993). Childhood asthma and indoor environmental risk factors. Am J Epidemiol 137(8):834-44.

Infante-Rivard C, Gautrin D, Malo JL, Suissa S (1999). Maternal smoking and childhood asthma. Am J Epidemiol 150(5):528-31.

Iribarren C, Friedman GD, Klatsky AL, Eisner MD (2001). Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. J Epidemiol Community Health 55(10):721-8.

Iversen M, Birch L, Lundqvist GR, Elbrond O. (1985). Middle ear effusion in children and the indoor environment: an epidemiological study. Arch Environ Health. 40(2):74-9.

Jaakkola MS, Piipari R, Jaakkola N, Jaakkola JJ. (2003). Environmental tobacco smoke and adult-onset asthma: a population-based incident case-control study. Am J Public Health. 93(12):2055-60.

Jaakkola JJ, Nafstad P, Magnus P (2001). Environmental tobacco smoke, parental atopy, and childhood asthma. Environ Health Perspect 109(6):579-82.

Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P (1996). Effect of passive smoking on the development of respiratory symptoms in young adults: an 8-year longitudinal study. J Clin Epidemiol 49(5):581-6.

Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P. (1995). Passive smoking and evolution of lung function in young adults. An 8-year longitudinal study. J Clin Epidemiol. 48(3):317-27; ISSN: 0895-4356.

Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P (2001). Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 358(9299):2103-9.

Jedrychowski W, Flak E (1997). Maternal smoking during pregnancy and postnatal exposure to environmental tobacco smoke as predisposition factors to acute respiratory infections. Environ Health Perspect 105(3):302-6.

Jin C, Rossignol AM (1993). Effects of passive smoking on respiratory illness from birth to age eighteen months, in Shanghai, People's Republic of China. J Pediatr 123(4):553-8.

Jindal SK, Jha LK, Gupta D (1999). Bronchial hyper-responsiveness of women with asthma exposed to environmental tobacco smoke. Indian J Chest Dis Allied Sci 41(2):75-82.

Jones RC, Hughes CR, Wright D, Baumer JH (1999). Early house moves, indoor air, heating methods and asthma. Respir Med 93(12):919-22.

Jones S, Love C, Thomson G, Green R, Howden-Chapman P (2001). Second-hand smoke at work: the exposure, perceptions and attitudes of bar and restaurant workers to environmental tobacco smoke. Aust N Z J Public Health 25(1):90-3.

Junker MH, Danuser B, Monn C, Koller T (2001). Acute sensory responses of nonsmokers at very low environmental tobacco smoke concentrations in controlled laboratory settings. Environ Health Perspect 109(10):1045-52.

Kauffmann F, Dockery DW, Speizer FE, Ferris BG Jr (1989). Respiratory symptoms and lung function in relation to passive smoking: a comparative study of American and French women. Int J Epidemiol 18(2):334-44.

Kawachi I, Colditz GA, Speizer FE, Manson JE, Stampfer MJ, Willett WC, Hennekens CH. (1997). A prospective study of passive smoking and coronary heart disease. Circulation 95(10):2374-9.

Kendirli GS, Altintas DU, Alparslan N, Akmanlar N, Yurdakul Z, Bolat B (1998). Prevalence of childhood allergic diseases in Adana, Southern Turkey. Eur J Epidemiol 14(4):347-50.

Kesavanathan J, Swift DL, Fitzgerald TK, Permutt T, Bascom R (1996). Evaluation of acoustic rhinometry and posterior rhinomanometry as tools for inhalation challenge studies. J Toxicol Environ Health 48(3):295-307.

Kivity S, Sade K, Abu-Arisha F, Lerman Y, Kivity S (2001). Epidemiology of bronchial asthma and chronic rhinitis in schoolchildren of different ethnic origins from two neighboring towns in Israel. Pediatr Pulmonol 32(3):217-21.

Kronqvist M, Johansson E, Pershagen G, Johansson SG, van Hage-Hamsten M (1999). Risk factors associated with asthma and rhinoconjunctivitis among Swedish farmers. Allergy 54(11):1142-9.

Kunzli N, Schwartz J, Stutz EZ, Ackermann-Liebrich U, Leuenberger P (2000). Association of environmental tobacco smoke at work and forced expiratory lung function among never smoking asthmatics and non- asthmatics. The SAPALDIA-Team. Swiss Study on Air Pollution and Lung Disease in Adults. Soz Praventivmed 45(5):208-17.

Lakshmipathy N, Bokesch PM, Cowen DE, Lisman SR, Schmid CH (1996). Environmental tobacco smoke: a risk factor for pediatric laryngospasm . Anesth Analg 82(4):724-7.

Lam TH, Chung SF, Betson CL, Wong CM, Hedley AJ (1998). Respiratory symptoms due to active and passive smoking in junior secondary school students in Hong Kong. Int J Epidemiol 27(1):41-8.

Lam TH, Hedley AJ, Chung SF, Macfarlane DJ (1999). Passive smoking and respiratory symptoms in primary school children in Hong Kong. Child Health and Activity Research Group (CHARG). Hum Exp Toxicol 18(4):218-23.

Lam TH, Leung GM, Ho LM (2001). The effects of environmental tobacco smoke on health services utilization in the first eighteen months of life. Pediatrics 107(6):E91.

Lanphear BP, Aligne CA, Auinger P, Weitzman M, Byrd RS (2001). Residential exposures associated with asthma in US children. Pediatrics 107(3):505-11.

Larsson ML, Frisk M, Hallstrom J, Kiviloog J, Lundback B (2001). Environmental tobacco smoke exposure during childhood is associated with increased prevalence of asthma in adults. Chest 120(3):711-7.

Leeder SR, Corkhill RT, Irwig LM, Holland WW (1976). Influence of family factors on asthma and wheezing during the first five years of life. Br J Prev Soc Med 30(4):213-8.

Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, Brandli O, Braun P, Bron C, Brutsche M, Domenighetti G, Elsasser S, Guldimann P, Holenstein C, Hufschmid P, Karrer W, Keller R, Keller-Wossidlo H, Kunzli N, Luthi JC, Martin BW, Medici T, Perruchoud AP, Radaelli A, Schindler C, Schoeni MH, Solari G, Tschopp JM, Villiger B, Wuthrich B, Zellweger JP, Zemp E. (1994). Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 150(5 Pt 1):1222-8.

Li JS, Peat JK, Xuan W, Berry G (1999). Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. Pediatr Pulmonol 27(1):5-13.

Li YF, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Rappaport EB, Peters JM. (2000). Effects of *in utero* and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. Am J Respir Crit Care Med 162(6):2097-104.

Lilienfeld AM, Lilienfeld DE. (1980). Foundations of Epidemiology (2nd Edition). New York: Oxford University Press.

Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, Nordvall SL (1995). Indoor environmental risk factors in young asthmatics: a case-control study. Arch Dis Child 73(5):408-12.

Lister SM, Jorm LR (1998). Parental smoking and respiratory illnesses in Australian children aged 0-4 years: ABS 1989-90 National Health Survey results. Aust N Z J Public Health 22 (7):781-6.

Liu KS, Alevantis LE, Offermann FJ (2001). A survey of environmental tobacco smoke controls in California office buildings. Indoor Air 11(1):26-34.

Lucas A, Brooke OG, Cole TJ, Morley R, Bamford MF (1990). Food and drug reactions, wheezing, and eczema in preterm infants. Arch Dis Child 65(4):411-5.

Macarthur C, Calpin C, Parkin PC, Feldman W (1996). Factors associated with pediatric asthma readmissions. J Allergy Clin Immunol 98(5 Pt 1):992-3.

McConnochie KM, Roghmann KJ (1986). Breast feeding and maternal smoking as predictors of wheezing in children age 6 to 10 years. Pediatr Pulmonol 2(5):260-8.

Maier WC, Arrighi HM, Morray B, Llewellyn C, Redding GJ (1997). Indoor risk factors for asthma and wheezing among Seattle school children. Environ Health Perspect 105(2):208-14.

Mannino DM, Homa DM, Redd SC (2002). Involuntary smoking and asthma severity in children: data from the Third National Health and Nutrition Examination Survey. Chest 122(2):409-15.

Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J (2001). Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Pediatr Adolesc Med 155(1):36-41.

Mannino DM, Siegel M, Rose D, Nkuchia J, Etzel R (1997). Environmental tobacco smoke exposure in the home and worksite and health effects in adults: results from the 1991 National Health Interview Survey. Tob Control 6(4):296-305.

Margolis PA, Keyes LL, Greenberg RA, Bauman KE, LaVange LM (1997). Urinary cotinine and parent history (questionnaire) as indicators of passive smoking and predictors of lower respiratory illness in infants. Pediatr Pulmonol 23(6):417-23.

Martinez FD, Cline M, Burrows B. (1992). Increased incidence of asthma in children of smoking mothers. Pediatrics. 89(1):21-6.

Masi MA, Hanley JA, Ernst P, Becklake MR (1988). Environmental exposure to tobacco smoke and lung function in young adults. Am Rev Respir Dis 138(2):296-9.

McDonnell WF , Abbey DE, Nishino N, Lebowitz MD (1999). Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study. Environ Res 80(2 Pt 1):110-21.

McWhorter WP , Polis MA, Kaslow RA (1989). Occurrence, predictors, and consequences of adult asthma in NHANESI and follow-up survey. Am Rev Respir Dis 139(3):721-4.

Meijer GG, Postma DS, van der Heide S, de Reus DM, Roorda RJ, Koeter GH, van Aalderen WM.. (1996). Exogenous stimuli and circadian peak expiratory flow variation in allergic asthmatic children. Am J Respir Crit Care Med 153(1):237-42.

Melen E, Wickman M, Nordvall SL, van Hage-Hamsten M, Lindfors A (2001). Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. Allergy 56(7):646-52.

Mizoue T, Reijula K, Andersson K (2001). Environmental tobacco smoke exposure and overtime work as risk factors for sick building syndrome in Japan. Am J Epidemiol 154(9):803-8.

Muramatsu T, Weber A, Muramatsu S, Akermann F (1983). An experimental study on irritation and annoyance due to passive smoking. Int Arch Occup Environ Health 51(4):305-17.

Nafstad P, Jaakkola JJ, Hagen JA, Botten G, Kongerud J (1996). Breastfeeding, maternal smoking and lower respiratory tract infections. Eur Respir J 9(12):2623-9.

National Research Council (1986). Environmental tobacco smoke: measuring exposures and assessing health effects. Washington D.C.: National Academy Press.

Nelson E, Goubet-Wiemers C, Guo Y, Jodscheit K (1999). Maternal passive smoking during pregnancy and foetal developmental toxicity. Part 2: histological changes. Hum Exp Toxicol 18(4):257-64.

Neuspiel DR, Rush D, Butler NR, Golding J, Bijur PE, Kurzon M (1989). Parental smoking and post-infancy wheezing in children: a prospective cohort study. Am J Public Health 79(2):168-71.

Ng TP, Hui KP, Tan WC (1993). Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. J Epidemiol Community Health 47(6):454-8.

Niewoehner DE, Kleinerman J, Rice DB (1974). Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 291(15):755-8.

Nowak D, Jorres R, Martinez-Muller L, Grimminger F, Seeger W, Koops F, Magnussen H. (1997a). Effect of 3 hours of passive smoke exposure in the evening on inflammatory markers in bronchoalveolar and nasal lavage fluid in subjects with mild asthma. Int Arch Occup Environ Health 70(2):85-93.

Nowak D, Jorres R, Schmidt A, Magnussen H (1997b). Effect of 3 hours' passive smoke exposure in the evening on airway tone and responsiveness until next morning. Int Arch Occup Environ Health 69(2):125-33.

O'Connor GT, Weiss ST, Tager IB, Speizer FE (1987). The effect of passive smoking on pulmonary function and nonspecific bronchial responsiveness in a population-based sample of children and young adults. Am Rev Respir Dis 135(4):800-4.

Oddoze C, Dubus JC, Badier M, Thirion X, Pauli AM, Pastor J, Bruguerolle B. (1999). Urinary cotinine and exposure to parental smoking in a population of children with asthma. Clin Chem 45(4):505-9.

Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, Kendall GE, Burton PR.. (1999). Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. BMJ 319(7213):815-9.

Ogston SA, Florey CD, Walker CH (1985). The Tayside infant morbidity and mortality study: effect on health of using gas for cooking. Br Med J (Clin Res Ed) 290(6473):957-60.

Ogston SA, Florey CD, Walker CH (1987). Association of infant alimentary and respiratory illness with parental smoking and other environmental factors. J Epidemiol Community Health 41(1):21-5.

Owen MJ, Baldwin CD, Swank PR, Pannu AK, Johnson DL, Howie VM (1993). Relation of infant feeding practices, cigarette smoke exposure, and group child care to the onset and duration of otitis media with effusion in the first two years of life. J Pediatr 123(5):702-11.

Paradise JL , Rockette HE, Colborn DK, Bernard BS, Smith CG, Kurs-Lasky M, Janosky JE. (1997). Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. Pediatrics 99(3):318-33.

Pedreira FA, Guandolo VL, Feroli EJ, Mella GW, Weiss IP (1985). Involuntary smoking and incidence of respiratory illness during the first year of life. Pediatrics 75(3):594-7.

Peters J, Hedley AJ, Wong CM, Lam TH, Ong SG, Liu J, Spiegelhalter DJ. (1996). Effects of an ambient air pollution intervention and environmental tobacco smoke on children's respiratory health in Hong Kong. Int J Epidemiol 25(4):821-8.

Peters J, McCabe CJ, Hedley AJ, Lam TH, Wong CM (1998). Economic burden of environmental tobacco smoke on Hong Kong families: scale and impact. J Epidemiol Community Health 52(1):53-8.

Piipari R, Jaakkola JJ, Jaakkola N, Jaakkola MS (2004). Smoking and asthma in adults. Eur Respir J 24(5):734-9.

Ponsonby AL , Couper D, Dwyer T, Carmichael A, Kemp A, Cochrane J (2000). The relation between infant indoor environment and subsequent asthma. Epidemiology 11(2):128-35.

Raynal A, Burge PS, Robertson A, Jarvis M, Archibald M, Hawkins D (1995). How much does environmental tobacco smoke contribute to the building symptom index? Indoor Air 5:2-28.

Reese AC, James IR, Landau LI, Lesouef PN (1992). Relationship between urinary cotinine level and diagnosis in children admitted to hospital. Am Rev Respir Dis 146(1):66-70.

Richards GA, Terblanche AP, Theron AJ, Opperman L, Crowther G, Myer MS, Steenkamp KJ, Smith FC, Dowdeswell R, van der Merwe CA, Stevens K, Anderson R (1996). Health effects of passive smoking in adolescent children. S Afr Med J 86(2):143-7.

Rizzi M, Sergi M, Andreoli A, Pecis M, Bruschi C, Fanfulla F (2004) Environmental tobacco smoke may induce lung damage in healthy male adolescents. Chest 125:1387-93.

Robbins AS, Abbey DE, Lebowitz MD (1993). Passive smoking and chronic respiratory disease symptoms in non-smoking adults. Int J Epidemiol 22(5):809-17.

Ronmark E, Jonsson E, Platts-Mills T, Lundback B (1999). Different pattern of risk factors for atopic and nonatopic asthma among children--report from the Obstructive Lung Disease in Northern Sweden Study. Allergy 54(9):926-35.

Rumold R, Jyrala M, Diaz-Sanchez D (2001). Secondhand smoke induces allergic sensitization in mice. J Immunol 167(8):4765-70.

Rylander E, Pershagen G, Eriksson M, Bermann G (1995). Parental smoking, urinary cotinine, and wheezing bronchitis in children. Epidemiology 6(3):289-93.

Rylander R, Megevand Y (2000). Environmental risk factors for respiratory infections. Arch Environ Health 55(5):300-3.

Samet JM, Cain WS, Leaderer BP (1991). Environmental tobacco smoke. Indoor Air Pollution. Baltimore: Johns Hopkins University Press, p. 131-69.

Schappert SM (1992). Office visits for otitis media: United States, 1975-90. Adv Data (214):1-19.

Schilling RS, Letai AD, Hui SL, Beck GJ, Schoenberg JB, Bouhuys A (1977). Lung function, respiratory disease, and smoking in families. Am J Epidemiol 106(4):274-83.

Schwartz J, Timonen KL, Pekkanen J (2000). Respiratory effects of environmental tobacco smoke in a panel study of asthmatic and symptomatic children. Am J Respir Crit Care Med 161(3 Pt 1):802-6.

Selcuk ZT, Caglar T, Enunlu T, Topal T (1997). The prevalence of allergic diseases in primary school children in Edirne, Turkey. Clin Exp Allergy 27(3):262-9.

Shamssain MH, Shamsian N (1999). Prevalence and severity of asthma, rhinitis, and atopic eczema: the north east study. Arch Dis Child 81(4):313-7.

Shusterman D, Lipscomb J, Neutra R, Satin K (1991). Symptom prevalence and odor-worry interaction near hazardous waste sites. Environ Health Perspect 94:25-30.

Shusterman DJ, Murphy MA, Balmes JR (1998). Subjects with seasonal allergic rhinitis and nonrhinitic subjects react differentially to nasal provocation with chlorine gas. J Allergy Clin Immunol 101(6 Pt 1):732-40.

Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML (1999). Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. Chest 115(3):691-6.

Smyth A, O'Hea U, Feyerabend C, Lewis S, Smyth R. (2001). Trends in passive smoking in cystic fibrosis, 1993-1998. Pediatr Pulmonol. 31(2):133-7.

Stenstrom R, Bernard PA, Ben-Simhon H (1993). Exposure to environmental tobacco smoke as a risk factor for recurrent acute otitis media in children under the age of five years. Int J Pediatr Otorhinolaryngol 27(2):127-36.

Stoddard JJ , Miller T (1995). Impact of parental smoking on the prevalence of wheezing respiratory illness in children. Am J Epidemiol 141(2):96-102.

Strachan DP, Butland BK, Anderson HR (1996). Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 312(7040):1195-9.

Strachan DP, Carey IM (1995). Home environment and severe asthma in adolescence: a population based case-control study. BMJ 311(7012):1053-6.

Strachan DP, Jarvis MJ, Feyerabend C. (1989). Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. BMJ 298(6687):1549-52.

Strachan DP, Cook DG (1997). Health effects of passive smoking. 1. Parental smoking and lower respiratory illness in infancy and early childhood. Thorax 52(10):905-14.

Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P (2004) Parental smoking in childhood and adult obstructive lung disease: results from the European Community Respiratory Health Survey. Thorax 59:295-302.

Tager, I. B.; Weiss, S. T.; Munoz, A.; Rosner, B., and Speizer, F. E. (1983). Longitudinal study of the effects of maternal smoking on pulmonary function in children. N Engl J Med. 309(12):699-703.

Tariq SM, Hakim EA, Matthews SM, Arshad SH (2000). Influence of smoking on asthmatic symptoms and allergen sensitisation in early childhood. Postgrad Med J 76(901):694-9.

Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW (1998). The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study . J Allergy Clin Immunol 101(5):587-93.

Tarlo SM, Broder I, Corey P, Chan-Yeung M, Ferguson A, Becker A, Warren P, Simons FE, Sherlock C, Okada M, Manfreda J. (2000). A case-control study of the role of cold symptoms and other historical triggering factors in asthma exacerbations. Can Respir J 7(1):42-8.

Taylor B, Wadsworth J (1987). Maternal smoking during pregnancy and lower respiratory tract illness in early life. Arch Dis Child 62(8):786-91.

Thorn J, Brisman J, Toren K (2001). Adult-onset asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. Allergy 56(4):287-92.

Togias A (2000). Unique mechanistic features of allergic rhinitis. J Allergy Clin Immunol 105(6 Pt 2):S599-604.

Toren K, Brisman J, Jarvholm B (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. Chest 104(2):600-8.

U.S. Department of Commerce (2002). 2000 census of population: general population characteristics - California. Washington D.C.: U.S. Government Printing Office.

U.S. DHHS (1986). The health consequences of involuntary smoking. A report of the surgeon general. Washington D.C.: U.S. Government Printing Office. Report No.: PHS Publication No. CDC 87-8398.

U.S. DHHS (2004). The health consequences of smoking: a report of the surgeon general. Rockville, MD: U.S. Dept Health and Human Services, Public Health Service, Centers for Disease Control.

U.S. EPA (1992). Respiratory health effects of passive smoking: lung cancer and other disorders. Washington D.C.: U.S.EPA. Report No.: Publication No. EPA/600/6-90/006F.

Undem BJ, Kajekar R, Hunter DD, Myers AC (2000). Neural integration and allergic disease. J Allergy Clin Immunol 106(5 Suppl):S213-20.

Venners SA, Wang X, Chen C, Wang B, Ni J, Jin Y, Yang J, Fang Z, Weiss ST, Xu X.. (2001). Exposure-response relationship between paternal smoking and children's pulmonary function. Am J Respir Crit Care Med 164(6):973-6.

Victora CG, Fuchs SC, Flores JA, Fonseca W, Kirkwood B (1994). Risk factors for pneumonia among children in a Brazilian metropolitan area. Pediatrics 93(6 Pt 1):977-85.

Vinke JG, KleinJan A, Severijnen LW, Fokkens WJ (1999). Passive smoking causes an 'allergic' cell infiltrate in the nasal mucosa of non-atopic children. Int J Pediatr Otorhinolaryngol 51(2):73-81.

von Ehrenstein OS, Schaal W, Maier E, Roscher AA, Nicolai T, Weiland SK, Keil U, Leupold W, Irsch T, von Mutius E. (1999). Children with A1-antitrypsin deficiency and exposure to environmental tobacco smoke (ETS) have diminished lung function [Abstract]. 10. 10(4):S149.

Vork K, Broadwin R, Lipsett M (2002). Household environmental tobacco smoke (ETS) exposure and risk of childhood asthma - techniques to reduce between-study heterogeneity in a meta-analysis.

Walker JC, Nelson PR, Cain WS, Utell MJ, Joyce MB, Morgan WT, Steichen TJ, Pritchard WS, Stancil MW. (1997). Perceptual and psychophysiological responses of non-smokers to a range of environmental tobacco smoke concentrations. Indoor Air 7:173-88.

Wang TN, Ko YC, Chao YY, Huang CC, Lin RS (1999). Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. Environ Res 81(3):239-47.

Wennergren G, Amark M, Amark K, Oskarsdottir S, Sten G, Redfors S (1997). Wheezing bronchitis reinvestigated at the age of 10 years. Acta Paediatr 86(4):351-5.

Wieslander G, Lindgren T, Norback D, Venge P (2000). Changes in the ocular and nasal signs and symptoms of aircrews in relation to the ban on smoking on intercontinental flights. Scand J Work Environ Health 26(6):514-22.

Wiley JA, Robinson JP, Cheng Y-T, Piazza T, Stork L, Pladsen K. (1991). Study of children's activity patterns: Final report. Sacramento, CA: California Air Resources Board. Report No.: Contract No. A733-149.

Willers S, Axmon A, Feyerabend C, Nielsen J, Skarping G, Skerfving S (2000). Assessment of environmental tobacco smoke exposure in children with asthmatic symptoms by questionnaire and cotinine concentrations in plasma, saliva, and urine. J Clin Epidemiol 53 (7):715-21.

Willes SR, Fitzgerald TK, Permutt T, Proud D, Haley NJ, Bascom R (1998). Acute respiratory response to prolonged, moderate levels of sidestream tobacco smoke. J Toxicol Environ Health A 53(3):193-209.

Withers NJ, Low L, Holgate ST, Clough JB (1998). The natural history of respiratory symptoms in a cohort of adolescents. Am J Respir Crit Care Med 158(2):352-7.

Xu X, Li B (1995). Exposure-response relationship between passive smoking and adult pulmonary function. Am J Respir Crit Care Med 151(1):41-6.

Yang CY, Lin MC, Hwang KC (1998). Childhood asthma and the indoor environment in a subtropical area. Chest 114(2):393-7.

Yu M, Pinkerton KE, Witschi H (2002). Short-term exposure to aged and diluted sidestream cigarette smoke enhances ozone-induced lung injury in B6C3F1 mice. Toxicol Sci 65(1):99-106.

Zavras AI, al-Bultan T, Jackson A, White G (1997). Exposure to passive smoking and other predictors of reduced nasal volume in children 7 to 12 years old. J Clin Pediatr Dent 21(4):295-303.

Chapter 6. Respiratory Health Effects 6-1
6.0. Introduction 6-1
6.1. Lung Growth and Development (children) 6-2
6.1.1. New Epidemiological Findings 6-2
6.1.2. Studies on Lung Development in Animals 6-10
6.1.3. Summary of ETS Effects on Lung Growth and Development 6-11
6.2. Acute Health Effects in Children 6-12
6.2.1. Asthma Exacerbation 6-12
6.2.2. Respiratory Infections (children) 6-24
6.2.3. Otitis Media in Children) 6-38
6.3. Chronic Health Effects (Children) 6-48
6.3.1. Chronic Respiratory Symptoms (children) 6-48
6.3.2. Asthma Induction in Children 6-48
6.4. Acute Health Effects (Adults) 6-74
6.4.1. Asthma (exacerbation) 6-74

6.4.2. Sensory Irritation and Annoyance 6-81
6.5. Chronic Health Effects in Adolescents and Adults 6-93
6.5.1. Pulmonary Function Changes and Respiratory Symptoms 6-93
6.5.2. Asthma Induction in Adolescents and Adults 6-100
6.6. Susceptible Populations 6-112
6.6.1. ETS and Cystic Fibrosis 6-113
6.7. Chapter Summary and Conclusions 6-115
6.7.1. Effects of ETS on Children 6-115
6.7.2. Effects of ETS on Adults 6-116
6.8. References 6-118